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REVIEW

Glycosyltransferases and non-alcoholic fatty liver disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is the most common form of chronic liver disease and its incidence is increasing worldwide. However, the underlying mechanisms leading to the development of NAFLD are still not fully understood. Glycosyltransferases (GTs) are a diverse class of enzymes involved in catalyzing the transfer of one or multiple sugar residues to a wide range of acceptor molecules. GTs mediate a wide range of functions from structure and storage to signaling, and play a key role in many fundamental biological processes. Therefore, it is anticipated that GTs have a role in the pathogenesis of NAFLD. In this article, we present an overview of the basic information on NAFLD, particularly GTs and glycosylation modification of certain molecules and their association with NAFLD pathogenesis. In addition, the effects and mechanisms of some GTs in the development of NAFLD are summarized.

Key words: Non-alcoholic fatty liver disease; Pathogenesis; Glycosyltransferases; Glycosylation

Core tip: Nonalcoholic fatty liver disease (NAFLD) is characterized by a very complicated process which is regulated by a number of protein molecules. Glycosylation, one of the most common post-translational modifications of proteins in eukaryotic cells, has been suggested to play an important role in the pathogenesis of NAFLD. As glycosylation is mainly mediated through glycosyltransferases (GTs), it seems reasonable to speculate that the GTs play an important role in the pathogenesis of NAFLD.

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OVERVIEW OF NON-ALCOHOLIC FATTY LIVER DISEASE

Fatty liver is characterized by the excess accumulation of lipids including triglycerides (TGs) and cholesterol. In general, accumulation of lipids up to 5% of the liver weight results in the diagnosis of fatty liver disease or hepatic steatosis. In addition, if hepatic steatosis occurs in patients who do not consume alcohol on a daily basis, it is referred to as non-alcoholic fatty liver disease (NAFLD)[1]. Usually, NAFLD is classified as "primary" and "secondary", depending on the underlying etiology. "Primary" NAFLD is most common, and is often associated with insulin-resistance and metabolic syndrome. Obesity, diabetes and dyslipidemia are the most common risk factors for NAFLD. The term "secondary" NAFLD is currently discouraged and the preferred nomenclature is based on the known causative factors and the resultant pathologies *e.g.,* viral infections, autoimmune diseases, endocrine-metabolic disorders, total parenteral nutrition and drug-induced fatty liver. Therefore, the term "NAFLD" generally refers to "primary" NAFLD. The obesity and type 2 diabetes pandemic, and the improved management of chronic viral hepatitis have resulted in NAFLD being a leading cause of chronic liver disease[2-6]. It is estimated that 20% to 30% of adults in the United States and Western Europe have excess fat accumulation in the liver[7]. The prevalence of NAFLD in the general population across Asia varies from 5% to 40%[8]. A recent meta-analysis showed that the prevalence of NAFLD in China is approximately 20%[9]. With the increase in obesity and diabetes, the incidence of NAFLD is expected to rise worldwide. The prevalence of NAFLD in the United States is expected to increase by 50% in 2030[10]. Based on current information, NAFLD encompasses a spectrum of diseases ranging from simple steatosis, to inflammatory steatohepatitis (NASH) with increasing levels of fibrosis and ultimately cirrhosis[11,12]. NAFLD was initially believed to be a benign illness as its progression is quite slow and rarely results in a poor outcome. However, results from clinical studies have confirmed that NAFLD, if not properly controlled, may cause liver-related morbidity and mortality[13]. Cirrhosis is a severe disease leading to death[14], and patients with NAFLD not only progress to cirrhosis[15], but are also susceptible to cardiovascular disease/death, type 2 diabetes mellitus and diabetic nephropathy[16,17], which are dependent on the severity of liver injury[18,19]. Moreover, NAFLD has also been shown to increase the risk of colorectal cancer[20] and thus, may result in an increased overall mortality[21] (Figure 1). Although weight loss is believed to be effective in NAFLD treatment, adherence to lifestyle interventions is a limitation. Various studies have shown that of the patients scheduled for NAFLD treatment, only 15% achieved weight loss, but regained weight with time[22]. Although there is no approved drug therapy for NAFLD, many approaches appear to be beneficial, such as the use of insulin sensitizers, antioxidants and anti-inflammatory agents, and these seem to have promising effects in some patients[23,24].

NAFLD PATHOGENESIS

The pathogenesis of NAFLD has not been completely elucidated[25,26]. Based on available information, various researchers have proposed different hypotheses over time. The major hypotheses are as follows: (1) In 1998, Day *et al*[27] first proposed the "two-hit" hypothesis for the pathogenesis of NAFLD. The first hit represents the accumulation of lipids in hepatocytes and the induction of insulin resistance which is the key pathogenic factor for the development of hepatic steatosis. The second hit leads to hepatocyte injury, inflammation and fibrosis. Factors initiating the second hit are oxidative stress and subsequent lipid peroxidation, proinflammatory cytokines, adipokines and mitochondrial dysfunction; (2) In 2008, Jou *et al*[28] suggested the "three-hit" hypothesis. The first hit also involves the accumulation of lipids by the mechanisms described above. The second hit involves the initiation of an inflammatory response and cell death, while the third hit results in defective repair and the induction of a regenerative response by the proliferation and differentiation of hepatocyte progenitors; (3) In 2009, Polyzos *et al*[29] provided the "multi-hit process" hypothesis. The initial hit leads to the development of simple steatosis which subsequently renders hepatocytes susceptible to a variety of additional hits, eventually leading to NASH. These additional hits appear to be genetic or environmental perturbations leading to liver cell inflammation and necrosis with activation of the fibrogenic cascade. This results in the development of fibrosis or even cirrhosis in a minority of NAFLD patients. Insulin resistance (IR) and subsequent hyperinsulinemia are key pathogenetic factors in both simple steatosis and its subsequent progression to NASH; and (4) In 2010, Tilg *et al*[30] proposed the "multiple parallel hits" hypothesis for NAFLD and it has attracted wide attention from the research community. This hypothesis reflects more precisely the current knowledge of NASH[20,31]. According to this hypothesis, many parallel hits are derived from the gut and/or the adipose tissue that promote liver inflammation. Endoplasmic reticulum (ER) stress and its related signaling networks, adipocytokines/cytokines, and innate immunity are

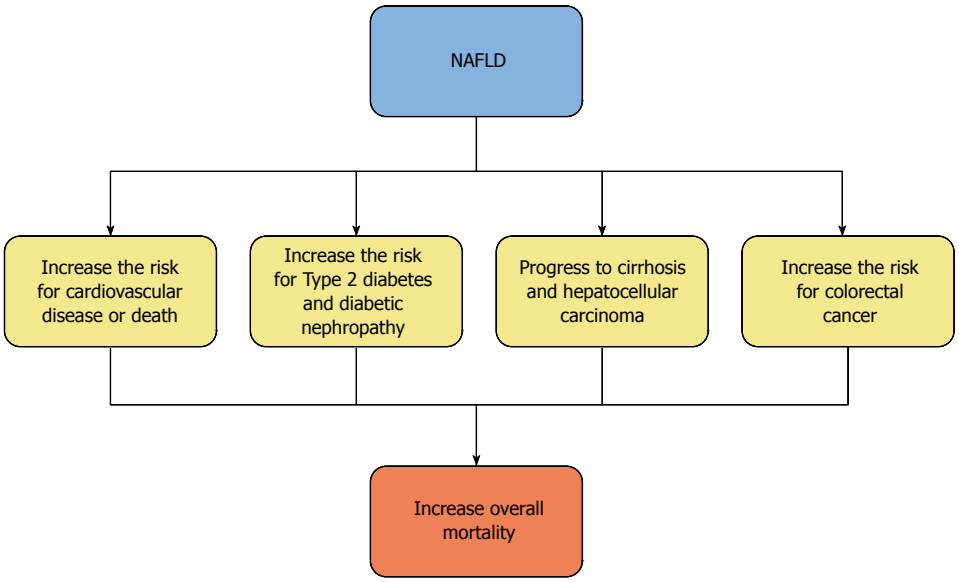

Figure 1 Manifestations of non-alcoholic fatty liver disease. NAFLD: Non-alcoholic fatty liver disease.

emerging as central pathways that regulate key features of NASH[32]. Although genetic factors play a minor role in the current obesity epidemic, they may offer explanations for a more progressive disease course in NAFLD[33]. Adipose tissue-derived factors include adipocytokines such as adiponectin and leptin, certain proinflammatory cytokines such as tumor necrosis factor α (TNF-α) or interleukin 6 (IL-6), and others such as the death receptor Fas, while gut-derived factors include endotoxin, microbiota, and various nutrients such as trans-fatty acids, fructose, and arylhydrocarbon receptor ligands. In addition, other proposed hypotheses are similar to the "multi-hit" hypothesis and four-step model[34,35].

MECHANISMS OF HEPATIC FAT ACCUMULATION

NAFLD is characterized by excess fat accumulation in the liver[36], which arises from an imbalance between fat acquisition and removal (Figure 2). TGs are composed of three fatty acids (FAs) coupled to a glycerol backbone *via* an ester bond. The fatty acids used for hepatic TGs formation are derived from three sources; (1) adipose tissue; (2) *de novo* lipogenesis (DNL); and (3) dietary sources[37]. Approximately 60% of liver FAs are derived from adipose tissue, 25% are from DNL, and 15% are from the diet[38]. FAs can be stored as lipid droplets within hepatocytes or secreted into the blood as very low-density lipoprotein (VLDL). However, they can also be channeled towards the β-oxidation pathway in mitochondria. Therefore, excess hepatic lipid accumulation can be caused by the following four different metabolic perturbations: (1) an increase in free fatty acid (FFA) uptake derived from the circulation due to increased lipolysis from adipose tissue and/or from the diet in the form of chylomicrons; (2) increased DNL; (3) reduced FA oxidation; and (4) reduced lipid export in the form of VLDL[39]. Rodent studies have shown that the mechanisms leading to excess accumulation of hepatic TGs are mainly associated with an increased supply of FFAs from peripheral adipose tissue to the liver and an enhanced *de novo* lipid synthesis *via* the lipogenic pathway[40]. Conversely, their disposal from the liver *via* β-oxidation and VLDL export are moderately affected[41]. Particularly in humans, obesity increases TNF-α production in adipocytes, facilitates adipocyte IR, and increases lipolysis rate. Thus, the circulating pool of FFAs is increased in obese individuals and thus accounts for the majority of the liver TGs in NAFLD. DNL refers to the synthesis of endogenous FAs in hepatocytes. During this process, glucose is converted to acetyl-CoA by glycolysis and the oxidation of pyruvate. Acetyl-CoA carboxylase then converts acetyl-CoA into malonyl-CoA and finally, FA synthase catalyzes the formation of palmitic acid from malonyl-CoA and acetyl-CoA. The rate of DNL is regulated primarily at the transcriptional level[42]. Several nuclear transcription factors are involved such as liver X receptors, sterol regulatory element-binding protein-1c (SREBP-1c), and carbohydrate-responsive element binding protein (ChREBP). SREBP-1c can regulate more than 32 genes involved in lipid biosynthesis and transport[43]. IR may promote DNL by stimulation of hyperinsulinemia to SREBP-1c[44]. Dietary fats taken up in the intestine are packaged into TG-rich chylomicrons and delivered to the systemic circulation. About 80% of the TG components in chylomicrons are unloaded in adipose and muscle tissues. The remaining 20% are transported to the liver through the hepatic artery[45]. As a result, the FAs derived from dietary fats account for the minority of circulating FFAs in NAFLD.

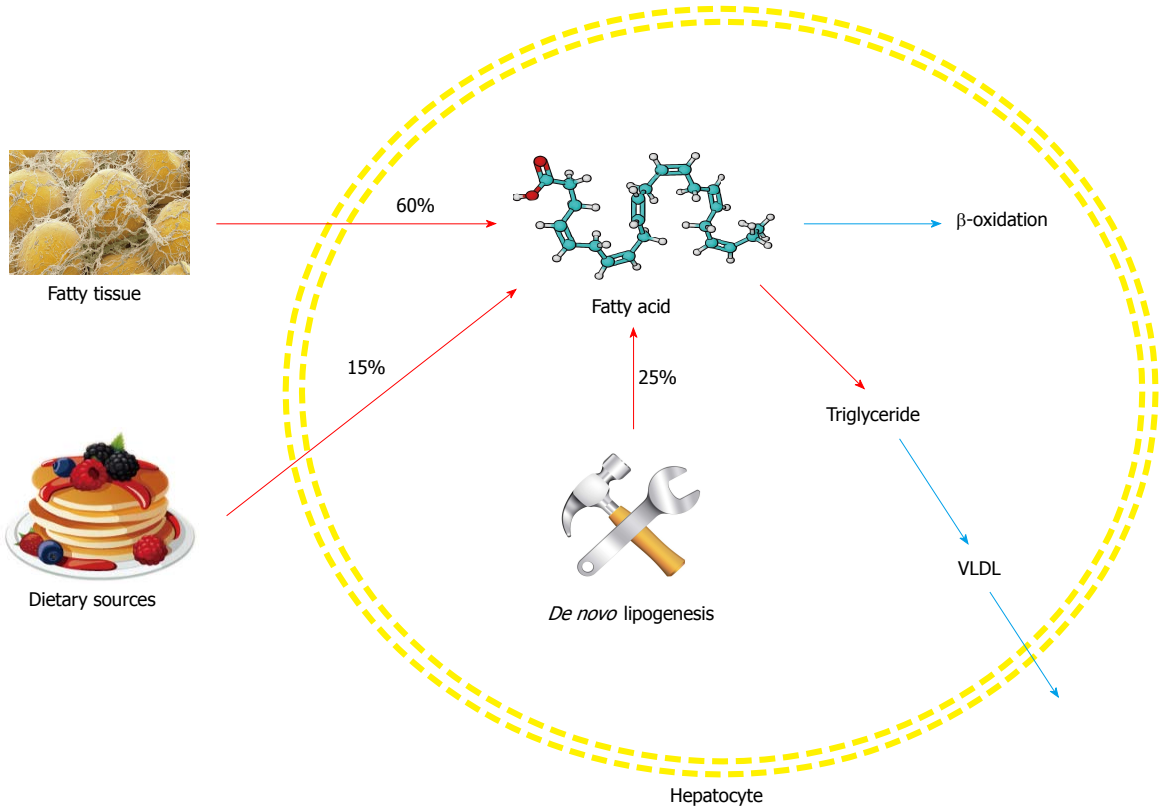

Figure 2 Mechanism of triglyceride accumulation in hepatocytes.

BASIC INFORMATION OF GLYCOSYLTRANSFERASES

Glycosyltransferases (GTs) are a diverse class of enzymes encompassing 1% to 2% of all sequenced genomes[46]. They catalyze the transfer of one or multiple sugar residues to a wide range of acceptor molecules such as lipids, proteins, hormones, secondary metabolites, and oligosaccharides[47,48], and mediate a wide range of functions from structure and storage to signaling[49]. Thus, they play a key role in many fundamental biological processes including cell signaling, cellular adhesion, carcinogenesis, and cell wall biosynthesis in human pathogens[50-52]. GTs are present in both prokaryotes and eukaryotes. In eukaryotes, the majority of GTs exist as membrane proteins of the Golgi apparatus. The newly synthesized GTs are transported from the ER to the Golgi *via* COP Ⅱ-transport vesicles[53,54]. All the Golgi-localized enzymes share the common topology of type Ⅱ membrane proteins, consisting of a short N-terminal cytoplasmic domain, a single transmembrane segment and a stem region of variable length followed by a large C-terminal catalytic domain[55,56]. The length and amino acid composition of catalytic domains are relatively well conserved and the variations in protein sizes are generally attributed to differences in the length of the stem region. In general, robust localization of Golgi enzymes relies on the contribution from each of these domains, although the transmembrane segment for a long time was considered to be the key determinant for GTs localization. The acceptor specificity may be regulated by the stem segment *in vivo*, although its role in enzyme activity is still unclear. The N-terminal domain is an important feature in acceptor binding. The significant variation in C-terminal β-strands and/or loops contributes to acceptor specificity and region specificity[57]. There are different classification systems for GTs: (1) GTs are primarily classified according to the type of sugar they transfer; (2) Based on sequence similarities of amino acids (CAZy database, http://www.cazy.org/), GTs are divided into 97 families. The vast majority of these sequences (more than 90%) are uncharacterized open-reading frames[58]; (3) X-ray structural studies have revealed that there are 105 GT structures in the Protein Data Bank, representing 36 of the 89 CAZy GT families[59], most of which adopt one of two predominant structural folds: GT-A and GT-B fold[60]. The GT-A fold consists of a single α/β/α-sandwich form that resembles a Rossmann fold. The central β-sheet is flanked by a smaller one, and the association of both creates the active site. A general feature of all the enzymes with GT-A fold is the presence of a common motif, such as the DXD motif[61,62]. The DXD motif anchors the pyrophosphate moiety of the sugar-nucleotide donor *via* a divalent cation, such that the location of the sugar donor on the fold is conserved. The GT-B fold

consists of two separate Rossmann domains with a connecting linker region and a catalytic site located between the domains. There is an excellent structural conservation between protein members of the GT-B family, particularly in the C-terminal domain which corresponds to the nucleotide-binding domain. A third family has recently emerged which comprises a bacterial sialyltransferase belonging to the GT42 family[63]. This protein displays a fold similar to the GT-A, but with some differences, thus it can be considered a new fold; and (4) Based on the outcome of the reaction, GTs are classified into two types, either inverting or retaining. Inverting GTs most likely follow a single displacement mechanism, wherein the acceptor induces a nucleophilic attack at carbon C-1 of the sugar donor somewhat analogous to the mechanism of inverting glycosidases. Retaining GTs do not operate *via* a two-step mechanism involving the formation of a glycosyl-enzyme intermediate analogous to glycosidases. Instead, an internal return SNi-like mechanism has been proposed, in which the departure of the leaving group and nucleophilic attack occur in a concerted, but asynchronous manner on the same face of the glycoside.

GLYCOSYLATION OF MOLECULES INVOLVED IN THE PATHOGENESIS OF NAFLD

Glycosylation is one of the most common post-translational modifications of proteins in eukaryotic cells[64,65]. Recent studies have indicated that numerous protein molecules undergoing glycosylation are involved in the pathogenesis of NAFLD.

Apolipoprotein B

The major function of VLDL is to transport endogenous TGs from the hepatocytes to the extrahepatic tissue. Apolipoprotein B (ApoB)-100, a large secretory glycoprotein with 4536 amino acid residues, is an important component of VLDL[66]. It has 19 potential glycosylation sites (Asn-X-Ser/Thr), and 16 of them have been reported to be glycosylated[67,68]. Ihara *et al*[69] reported that N-acetylglucosaminyltransferase Ⅲ (GnT-Ⅲ) is linked to the glycosylation of ApoB-100 in hepatocytes. Chylomicrons transport TGs from the gut to the periphery *via* intestinal lymph and the systemic circulation. ApoB-48 is a truncated segment of ApoB-100 and is homologous to the initial 2151 amino acids of ApoB-100. Studies have also confirmed that ApoB-48 can be modified by glycosylation[70,71].

Fatty acid translocase

Fatty acid uptake into the liver contributes to the steady balance of hepatic TGs in the liver, as well as the pathogenesis of NAFLD. The cellular capacity for fatty acid uptake depends on the numbers and activities of transporter proteins on the sinusoidal plasma membrane of the hepatocytes. Fatty acid translocase is a transporter protein, and is heavily modified post-translationally by N-linked glycosylation. The 10 putative glycosylation sites located in the large extracellular loop of the protein have been identified[72].

ChREBP

ChREBP is involved in the transcriptional activation of genes encoding the aforementioned rate-limiting enzymes in lipogenesis, and has been associated with increased DNL in NAFLD[73]. Guinez *et al*[74] reported that ChREBP interacts with *O*-GlcNAcylation transferase and is subjected to *O*-GlcNAcylation in liver cells which in turn stabilizes it and enhances its transcriptional activity toward its target glycolytic and lipogenic genes when combined with an active glucose flux *in vivo*.

Fas

Hepatocyte apoptosis is the most common and well-characterized cell death pathway. Hepatic apoptosis is also confirmed to be a pathologic hallmark of NASH[75]. Alkhouri *et al*[76] reported that there was an increased sensitivity to Fas-mediated hepatocyte apoptosis in a dietary model of NAFLD, when mice were fed a high-fat diet. In addition, liver tissue samples from NASH patients displayed high expression of Fas protein, suggesting that it plays a role in the development of NASH. Fas is a glycosylated protein, and undergoes glycosylation in its extracellular domain during NASH[77,78].

Adiponectin

Adiponectin is an insulin-sensitizing adipocytokine that has multiple beneficial effects in obesity-related NAFLD[79]. The collagenous region of adiponectin, produced *in vitro,* contains four conserved lysines that are both hydroxylated and glycosylated with a glucosylgalactosyl moiety[80]. In addition, bovine and mouse plasma adiponectin contains sialic acid, possibly on *O*-linked glycans[81].

EFFECT AND MECHANISM OF GTs ON THE DEVELOPMENT OF NAFLD

In recent years, a number of studies have demonstrated the role of some GTs in the development of NAFLD and their different mechanisms of action.

GnT-Ⅲ

GnT-Ⅲ is a key enzyme in N-glycan biosynthesis, encoded by the *Mgat3* gene[82], and is a mammalian Golgi-resident GT. It catalyzes the attachment of the bisecting GlcNAc residue to β-1, 4 mannose in the core structure of N-linked oligosaccharides[83]. Bisected N-glycans are involved in physiological and pathological processes through the functional regulation of their

carrier proteins[84,85]. Human GnT-Ⅱ contains 531 amino acids and possesses a domain structure identical to GTs[86]. The structure includes a short N-terminal cytoplasmic tail, a transmembrane region of 16-20 amino acids (as predicted by hydropathy plots), a stem region (or neck region), and a long C-terminal catalytic domain[87]. Ihara *et al*[69] found that the livers of *GnT-Ⅲ* transgenic mice contained abundant lipid droplets accompanied by ballooning degeneration. Although the levels of immunoreactive ApoB were increased, the ApoB-100 was specifically decreased to undetectable levels in the serum of these transgenic mice. These results strongly suggest that aberrant glycosylation of ApoB activated by GnT-Ⅲ inhibits the ApoB assembly itself and further blocks the synthesis and secretion of VLDL, which in turn leads to an accumulation of TGs within the liver.

T-synthase

T-synthase is the key β3-galactosyltransferase essential for the biosynthesis of core 1 *O*-glycans (Galβ1-3GalNAcα1-Ser/Thr) in the glycoproteins of animal cells[88]. It was initially purified from rat liver and subsequently cloned into the cDNA, and the genes for T-synthase were successfully identified from *Caenorhabditis elegans,* mouse, rat and human. The cDNA for T-synthase in mammals encodes a 363-amino acid transmembrane protein with type Ⅱ topology[89]. A decrease in the expression of T-synthase alters *O*-glycan elongation and results in the production of abnormal and truncated carbohydrate structures, eventually leading to exposure of the Tn antigen[90]. This has been shown to be associated with several human diseases, including cancer, Tn syndrome and IgA nephropathy[91]. A recent study showed that T-synthase knockout in endothelial and hematopoietic cells (EHC T-syn$^{-/-}$) of pups, resulted in the development of fatty liver disease in mice. Fu *et al*[92] reported that immediately after the pups began nursing on milk, the liver of postnatal 1 wk EHC T-syn$^{-/-}$ mice displayed an abnormal accumulation of vacuoles containing TGs, resembling microvesicular steatosis in human steatohepatitis. At postnatal 7 wk, the livers of EHC T-syn$^{-/-}$ mice, had extensive steatosis, inflammatory infiltrates, and hepatocyte ballooning. EHC T-syn$^{-/-}$ mice that survived beyond neonatal development displayed cirrhosis. EHC T-syn$^{-/-}$ adult mice were not obese. The lymphatic system is essential for the transport of immune cells, interstitial fluids, and dietary lipids[93]. Dietary lipids are transported in the form of chylomicrons from the small intestine to the systemic circulation *via* the intestinal lymphatic vessels and thoracic duct[94]. In EHC T-syn$^{-/-}$ mice, due to aberrant intestinal vein and lymphatic connections, chylomicrons are directly transported to the liver *via* the portal vein system, which causes fatty liver disease. Endothelial O-glycans control the separation of blood and lymphatic vessels during embryonic and postnatal development by regulating podoplanin expression. The abnormal O-glycosylation of endothelial podoplanin is sufficient for the formation of hybrid vessels and blood/lymphatic vessel misconnections. Therefore, the impairment of podoplanin expression/function by specific deletion of T-synthase may contribute to the aberrant connections between intestinal blood and lymphatic vessels.

α1, 6-fucosyltransferase

α1, 6-fucosyltransferase (FUT8) catalyzes the transfer of a fucosyl residue from guanine nucleotide diphosphate-β-l-fucose to the innermost GlcNAc of an asparagine-linked oligosaccharide[95]. It plays an important role in the tumorigenesis of non-small cell lung cancer and colon carcinoma[96,97]. Human *Fut8* gene is located on chromosome 14q23.3, and consists of at least nine exons spanning more than a 50 kb genomic region, and the coding sequence is divided into eight exons[98,99]. FUT8 is a typical type Ⅱ membrane protein localized in the Golgi apparatus[100]. It consists of 575 amino acids, and contains a catalytic domain, an N-terminal coiled-coil domain and a C-terminal SH3 domain. The catalytic domain was structurally classified as a member of the GT-B group of GTs. Wang *et al*[101] reported that lipid droplets in hepatocytes were significantly increased in the liver of FUT8 transgenic mice, and these lipid droplets were apparently localized within the lysosomes. Furthermore, the study showed that liver lysosomal acid lipase (LAL) activity was significantly lower in these transgenic mice compared to wild-type mice, and the level of fucosylated LAL was greater in transgenic mice. These results suggested that aberrant fucosylation of LAL causes an accumulation of inactive LAL in the lysosomes, and results in steatosis in the lysosomes of the liver in the case of FUT8 transgenic mice.

Glycosyltransferase 8 domain containing 2

As a member of the glycosyltransferase 8 family, the human glycosyltransferase 8 domain containing 2 (Glt8D2) is a 349 amino acid single-pass type Ⅱ membrane protein encoded by a gene located on chromosome 12q23.3. The first six amino acid residues extend to the cytoplasm, residues 7-24 constitute the transmembrane domain and residues 25-349 are in the luminal compartments[102]. Moylan *et al*[103] reported that the *GLT8D2* gene is up-regulated in patients with severe NAFLD. Recently, we have cloned the *GLT8D2* gene and found that GLT8D2 expression increased in fatty liver compared with normal liver in rats. Our *in vitro* study found that GLT8D2 expression increased in steatosis HepG2 cells compared with normal cells. In addition, further study showed that plasmid transfection of GLT8D2 increased the TG content, up-regulated ApoB-100 protein, but down-regulated microsomal triglyceride transfer protein

(MTP) in HepG2 cells. MTP has both apoB 100 binding and lipid transfer domains[104], and is an essential factor for VLDL assembly and secretion. As a result, we speculate that the inhibition of MTP expression by GLT8D2 may be the major mechanism resulting in accumulation of TG in HepG2 cells.

UDP-glucuronosyltransferases

UDP-glucuronosyltransferases (UGTs) are glycoproteins localized in the ER which catalyze the conjugation of a wide variety of lipophilic aglycon substrates with glucuronic acid using UDP-glucuronic acid as the sugar donor[105]. The human UGTs are membrane proteins with approximately 530 amino acids, of which the first 25 residues of the signal sequence are removed after the transfer of newly synthesized polypeptides to the ER. A single transmembrane helix is predicted close to the C terminus of the protein, and the membrane topology is such that the bulk of the protein is on the luminal side of the ER membrane[106]. The mammalian UGT gene superfamily currently has 117 members. On the basis of amino acid sequence similarity, the UGT superfamily is divided into four families, UGT1, UGT2, UGT3 and UGT8[107], and further subdivided into different subfamilies, respectively. It is well-known that UGTs are highly expressed in the liver, and induced by microsomal enzyme treatment through nuclear receptor- and transcription factor-dependent mechanisms[108,109]. In recent years, it was found that the UGT expression is abnormal in the liver of NAFLD subjects. Xu *et al*[110] reported that the mRNA expression of some of the UGT isoforms was increased in steatotic liver of ob/ob mice, and this was accompanied by increased mRNA expression of the arylhydrocarbon receptor, constitutive androstane receptor, peroxisome proliferator-activated receptor-α, pregnane X receptor, nuclear factor-like 2, and peroxisome proliferator-activated receptor-γ coactivator-1α. Zhang *et al*[111] also confirmed that fatty liver in rats on a high-fat diet showed increased mRNA and protein expression of UGT, and it was further enhanced by the addition of valproic acid. The induction of UGTs was accompanied by the increased expression of constitutive androstane receptor and peroxisome proliferator-activated receptor α. However, Hardwick *et al*[112] found that the expression of different UGT isoforms in the liver appears to be differentially regulated in human NASH. Hence, the role of UGT expression in NAFLD remains unclear. In addition, UGT also has a role in glucuronidation, which is a major detoxification pathway for exogenous compounds and is becoming increasingly important for metabolizing approximately 40%-70% of drugs[113]. Numerous xenobiotics, including acetaminophen, morphine, propofol, chloramphenicol, and nonsteroidal anti-inflammatory drugs, as well as environmental compounds, are glucuronidated by UGT[114]. Thus, it is possible that a UGT abnormality may exacerbate the side effects of the above drugs in NAFLD patients. Therefore, UGT abnormalities may also play an important role in the pathogenesis of NAFLD.

CONCLUSION

NAFLD is the most highly prevalent chronic liver disease, and its detailed mechanism remains unclear. TGs, which play an important role in many fundamental biological processes, are also confirmed to affect the development of NAFLD and play an important role in its pathogenesis. In addition, some molecules related to the pathogenesis of NAFLD are glycosylated and are modified by some GTs. However, many questions related to protein glycosylation and its role in the development of NAFLD have yet to be clarified. The precise mechanism of hepatic steatotic injury involving protein glycosylation and consequent NAFLD require further detailed investigation.

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