Austin Hepatology

Open Access

Austin Publishing Group

Mini Review

Molecular Pathways in Non-Alcoholic Fatty Liver Disease: An Emerging Menace

Suma D, Vysakh A and Latha MS*

School of Biosciences, Mahatma Gandhi University, Priyadarshini Hills, Kottayam, Kerala, India

***Corresponding author:** MS Latha, School of Biosciences, Mahatma Gandhi University, Priyadarshini Hills, Kottayam, Kerala, India

Received: November 18, 2016; **Accepted:** January 09, 2017; **Published:** January 11, 2017

Abstract

The liver is the largest glandular organ in the body and performs multiple critical functions to keep the body pure of toxins and harmful substances. Non-Alcoholic Fatty Liver Disease (NAFLD) is a clinicopathological change characterized by the accumulation of triglycerides (TG) in hepatocytes. It has frequently been associated with obesity, hyperlipidemia, type 2 diabetes mellitus (DM) and insulin resistance. Increased incidence of obesity in the modern society promotes insulin resistance in the peripheral tissues in humans and could cause severe metabolic disorders by inducing accumulation of lipid in the liver, resulting in the progression of NAFLD. It could lead to more severe diseases such as non-alcoholic steatohepatitis (NASH), cirrhosis and in some cases Hepatocellular Carcinoma (HCC). Accumulation of lipid in the liver can be traced by increased uptake of free fatty acids (FFAs) into the liver, impaired fatty acid beta oxidation or the increased incidence of de novo lipogenesis. Nowadays, a more complex model suggests that fatty acids (FAs) and their metabolites may be the true lipotoxic agents that contribute to NAFLD progression. This mini-review discusses the molecular mechanisms that contribute to NAFLD.

Keywords: Non-alcoholic fatty liver disease (NAFLD); Non-alcoholic steatohepatitis (NASH); De novo lipogenesis; Free fatty acids (FFAs); TG secretion

Introduction

NAFLD is a clinicopathological condition as stated here, can progress to a wide spectrum of liver damage, ranging from steatosis alone to steatohepatitis, advanced fibrosis and cirrhosis. The pathological condition resembles alcohol-induced liver injury, but NAFLD occurs in patients who do not consume significant amounts of alcohol. NASH represents only a stage in the spectrum of NAFLD and is defined pathologically by the presence of steatosis together with necro-inflammatory activity, mostly with an uneven lobular distribution, with or without fibrosis. Furthermore, lipid accumulation in the liver is also linked with the progression of endoplasmic reticulum stress (ER stress), mitochondria stress and impaired autophagy, resulting in the condition known as lipotoxicity. This latter event can cause the immune response in the Kupffer cells and hepatic stellate cells, which leads to the progression of NASH, hepatic cirrhosis and in some severe cases, HCC. The clinical implications of NAFLD are derived mostly from its potential to progress to end-stage liver disease, whereas simple uncomplicated steatosis follows a relatively benign course in most patients [1]. Because there are currently no effective therapies for NAFLD apart from weight loss, ongoing research efforts are focused on understanding the pathobiology of hepatic steatosis with the intention of identifying novel therapeutic targets. In this context, this mini- review analyses some of the molecular mechanisms that underlie the pathophysiological changes of hepatic lipid metabolism in NAFLD [2].

Fatty Acids Uptake

FFAs in the plasma can be taken up by the liver and serve as key sources for its TG synthesis. Normally, plasma FFAs are generated by white adipocytes via lipolysis, which is induced by beta adrenergic receptor agonists such as catecholamine under fasting conditions [3]. Fatty acid transporter protein (FATP), caveolins, fatty acid translocase (FAT)/CD36 and fatty acid binding protein (FABP) are the main plasma membrane transporters for FFA. There are 6 members of FATPs found in mammals that contain a common motif for fatty acid uptake and fatty acyl-CoA synthetase function. On the other hand, expression of FABP4 and FABP5 in the liver is correlated with hepatic fatty infiltration in NAFLD patients [4]. Further studies are needed to integrate roles of these fatty acid transporters in the hepatic FFA uptake under the physiological and pathological conditions [5].

De novo lipogenesis

De novo lipogenesis is an integrated metabolic pathway that comprises of the conversion of glucose to acetyl-CoA (glycolysis), biosynthesis of saturated fatty acid followed by desaturation and the formation of TG. Key rate limiting enzymes in the above mentioned pathways include glucokinase and liver-type pyruvate kinase in the glycolysis, acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS) in the fatty acid synthesis, long chain fatty acid elongase 6 (ELOVL6) and Stearoyl-CoA Desaturase (SCD) in the formation of monounsaturated fatty acids and glycerol-3-phosphate acyltransferase (GPAT), lipins and acyl-CoA: Diacylglycerol Acyltransferase (DGAT) in the formation of TG [6]. Sterol Regulatory Element Binding Protein 1c (SREBP-1c) and Carbohydrate Response Element Binding Protein (CHREBP), are the two major transcription factors for lipogenesis, which are involved in the transcriptional activation of genes encoding aforementioned rate-limiting enzymes in the lipogenesis and have been associated with increased de novo lipogenesis in NAFLD [6].

Citation: Suma D, Vysakh A and Latha MS. Molecular Pathways in Non-Alcoholic Fatty Liver Disease: An Emerging Menace. Austin Hepatol. 2017; 2(1): 1005.

In obese, insulin-resistant ob/ob mice, SREBP-1c and CHREBP are highly abundant in the liver, where reduction of either of them was shown to be beneficial in relieving hepatic steatosis in mice, underscoring the relevance of these lipogenic transcription factors in de novo lipogenesis and the TG accumulation in the liver [7].

Fatty acid oxidative pathways

Beta oxidation of fatty acid in mitochondria is a process to shorten the fatty acids into acetyl-CoA, which can be further converted into ketone bodies (beta hydroxybutyrate or acetoacetate) or can be incorporated into the TCA cycle for the complete oxidation. Indeed, mice deficient in MCAD and VLCAD develop hepatic steatosis, supporting the role of these proteins and the fatty acid beta oxidation in the hepatic TG content. 2-enoyl-CoA hydratase, 3-hydroxyacyl-CoA dehydrogenase and 3-oxoacyl-CoA thiolase are the three enzymes which subsequently are involved in the fatty acid beta oxidation process to complete the conversion of acyl-CoA ester into acetyl-CoA [8]. The clinical implication of impaired mitochondrial beta oxidation on the progression of NAFLD is not conclusive and contradicting reports have been published. Further studies are necessary to establish the role of fatty acid beta oxidation on hepatic lipid accumulation and the progression of NAFLD [9].

TG Secretion

In the liver, TG secretion is achieved via the formation of very low density lipoprotein (VLDL). VLDL consists of hydrophobic core lipids containing TGs and cholesterol esters, which are covered by hydrophilic phospholipids and apolipoprotein B (apoB) 100. ApoB 100 is a liver-specific ApoB that is critical in the VLDL assembly, while apoB 48 in the intestine is associated with chylomicron formation [10]. Indeed, hepatic steatosis was reported in patients carrying mutations in apoB 100 (hypobetalipoproteinemia) and in MTP (abetalipoproteinemia), indicating the importance of these proteins in the lipid homeostasis in humans [11].

Insulin plays a key role in the degradation of apoB 100, perhaps utilizing an autophagy-dependent pathway. Upon insulin resistance, perturbation of this process results in hypertriglyceridemia via increased TG secretion. However, the rate of TG secretion cannot keep up with the increased rate of TG synthesis in this condition, resulting in the hepatic steatosis in spite of the increased VLDL secretion. Similar phenotype is observed in NAFLD patients, which exhibit both hypertriglyceridemia and hepatic steatosis. Prolonged exposure of the liver to FFA would promotes ER stress and other oxidative stress in the liver, leading to the degradation of apoB 100, decrease in the VLDL secretion and worsening of hepatic steatosis [12].

Conclusion

This mini review reveals the balance between the TG uptake/synthesis and TG hydrolysis/secretion that is critical in the maintenance of lipid homeostasis in the liver. In the case of NAFLD, the progression of hepatic steatosis can stem from the increased FFA uptake, de novo lipogenesis leading to increased TG synthesis and the decreased TG hydrolysis, fatty acid beta oxidation leading to decreased TG secretion. Furthermore, Reduced TG secretion via VLDL could also promote hepatic lipid accumulation, although the VLDL secretion is rather increased in NAFLD patients. Lastly understanding molecular mechanisms of each pathway is crucial in pursuing the development of therapeutics of NAFLD in the future.

References

1. Alba LM, Lindor K. Non-alcoholic fatty liver disease. Alimentary pharmacology & therapeutics. 2003; 17: 977-986.
2. Berlanga A, Guiu-Jurado E, Porras JA, Auguet T. Molecular pathways in non-alcoholic fatty liver disease. Clin Exp Gastroenterol. 2014; 7: 221-239.
3. Arner P. Human fat cell lipolysis: biochemistry, regulation and clinical role. Best practice & research Clinical endocrinology & metabolism. 2005; 19: 471-482.
4. Westerbacka J, Kolak M, Kiviluoto T, Arkkila P, Sirén J, Hamsten A, et al. Genes involved in fatty acid partitioning and binding, lipolysis, monocyte/macrophage recruitment, and inflammation are over expressed in the human fatty liver of insulin-resistant subjects. Diabetes. 2007; 56: 2759-2765.
5. Towle HC, Kaytor EN, Shih HM. Regulation of the expression of lipogenic enzyme genes by carbohydrate. Annual review of nutrition. 1997; 17: 405-433.
6. Postic C, Girard J. Contribution of de novo fatty acid synthesis to hepatic steatosis and insulin resistance: lessons from genetically engineered mice. The Journal of clinical investigation. 2008; 118: 829-838.
7. Dentin R, Benhamed F, Hainault I, Fauveau V, Foufelle F, et al. Liver-specific inhibition of CHREBP improves hepatic steatosis and insulin resistance in ob/ob mice. Diabetes. 2006; 55: 2159-2170.
8. Tolwani RJ, Hamm DA, Tian L, Sharer JD, Vockley J, et al. Medium-chain acyl-CoA dehydrogenase deficiency in gene-targeted mice. PLoS Genet. 2005; 1: e23.
9. Samuel VT, Shulman GI. Mechanisms for insulin resistance: common threads and missing links. Cell. 2012; 148: 852-871.
10. Hussain MM, Shi J, Dreizen P. Microsomal triglyceride transfer protein and its role in apoB-lipoprotein assembly. Journal of lipid research. 2003; 44: 22-32.
11. Tanoli T, Yue P, Yablonskiy D, Schonfeld G. Fatty liver in familial hypobetalipoproteinemia: roles of the APOB defects, intra-abdominal adipose tissue, and insulin sensitivity. J Lipid Res. 2004; 45: 941–947.
12. Choi SH, Ginsberg HN. Increased very low density lipoprotein (VLDL) secretion, hepatic steatosis, and insulin resistance. Trends in Endocrinology & Metabolism. 2011; 22: 353-363.

Austin Hepatol - Volume 2 Issue 1 - 2017
Submit your Manuscript | www.austinpublishinggroup.com

Citation: Suma D, Vysakh A and Latha MS. Molecular Pathways in Non-Alcoholic Fatty Liver Disease: An Emerging Menace. Austin Hepatol. 2017; 2(1): 1005.