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Endoplasmic reticulum stress related molecular mechanisms in nonalcoholic steatohepatitis

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ABSTRACT

Nonalcoholic steatohepatitis (NASH) is considered to be a common health problem since the incidence of nonalcoholic fatty liver disease (NAFLD) has increased in recent years. Disturbed hepatic cholesterol homeostasis and free cholesterol accumulation in liver results in increased oxidative stress leading to the endoplasmic reticulum (ER) stress. Activated ER stress maintains protein homeostasis however, delayed or inadequate ER stress responses may induce fat accumulation, insulin resistance, inflammation, apoptosis, and autophagy, all of which increase with age and play crucial roles in the pathogenesis of NASH. In aging research, there is a growing interest for the role of ER stress in the progression of NASH since aging seems to favor NAFLD according to its pathogenesis. On the other hand, specific microRNAs (miRNAs) expression profiles are strongly related with ER stress as well as NASH progresses. This review highlights molecular mechanisms related to ER stress in the pathogenesis of NASH and miRNAs for the progression and treatment of the disease.

Contents

Abbreviations: ACC, acetyl-CoA carboxylase; AP-1, activator protein-1; ATF-4, activating transcription factor-4; ATF-6, activating transcription factor-6; AMPK, AMP-activated protein kinase; ApoA1, apolipoprotein A1; ABCA1, ATP Binding Cassette A1; ABCG4, ATP Binding Cassette G4; ABCG5/G8, ATP Binding Cassette G5/G8; Bcl-2, B-cell leukemia/lymphoma 2; BiP, binding immunoglobulin protein; CHOP, C/EBP homologous protein; nCEH, Cholesterol ester hydrolase; CYP7A1, cytochrome P450 7A1; ER, endoplasmic reticulum; ERAD, endoplasmic reticulum-associated protein degradation; eiF2α, eukaryotic translation initiation factor 2α; FAS, fatty acid synthase; FC, free cholesterol; FFAs, free fatty acids; GRP78, glucose-regulated protein 78; GADD34, growth arrest and DNA damage-inducible protein 34; HSC, hepatic stellate cells; HFD, high fat diet; HDL, high density lipoprotein; IRE1α, inositol requiring enzyme 1α; IR, insulin resistance; IL-6, interleukin-6; JNK, c-Jun N-terminal kinase; Keap1, kelch ECH associating protein 1; LC3-II, light chain 3-II; LXR-alpha, liver X receptor alpha; LDL, low density lipoprotein; LDLR, low density lipoprotein receptor; MCD, methionine/choline-deficient; miRNAs, MicroRNAs; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; Nrf2, nuclear factor 2 erythroid 2 -related factor; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; ox-LDL, oxidized low density lipoprotein; PPARα, peroxisome proliferator activated receptor-α; PPARγ, peroxisome proliferator activated receptor- γ; PTEN, phosphatase and tensin homolog; PERK, protein kinase RNA-activated (PKR)-like ER kinase; ROS, reactive oxygen species; SERCA, sarco(endo)plasmic reticulum Ca^{2+}-ATPase;; SR-BI, scavenger receptor class B type I; SCD1, stearoyl-CoA desaturase-1; SREBP-1c, sterol regulatory element-binding protein-1c; SREBP-2, sterol regulatory element-binding protein 2; TNF-α, tumor necrosis factor α; TRAF2, TNF-α receptor-associated factor 2; UPR, unfolded protein response; VLDL, very low density lipoprotein; XBP-1, X-box-binding protein-1.

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1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is a disorder characterized by fat accumulation (steatosis) in the liver, in the absence of chronic alcohol intake, viral infection or any other liver disease (Cohen et al., 2011). In some cases, steatosis progresses to a more severe form named as nonalcoholic steatohepatitis (NASH), which includes steatosis, inflammation, apoptosis and fibrosis and may progress to cirrhosis and hepatocellular carcinoma (De et al., 2013). Nowadays, NAFLD is recognized as the most common cause of chronic liver disease worldwide since the prevalence of NAFLD has doubled over the last twenty years (Kleiner and Brunt, 2012). It has been reported that the NAFLD may affect up 25% of the general population, which goes up to 90% of obese individuals. Additionally, NASH affects up to 3% of the general population that goes up to 37% of the obese population, makes the disease an emerging problem (Milic and Stimac, 2012).

NASH pathophysiology has been suggested as a "two-hit" process, (Gentile and Pagliassotti, 2008) in which, the first hit includes the development of hepatic steatosis by the accumulation of triglycerides in hepatocytes, while the second hit results from cellular stresses, such as oxidative stress, apoptosis and gut-derived microbiota, lipopolysaccharide and endotoxin stimulation. On the other hand, recently it has been suggested that patatin-like phospholipase 3 (PNPLA3) gene takes a role in NASH pathogenesis (Takaki et al., 2014). Findings about development of the disease, suggest that a two hit process is not enough to explain a heterogeneous disease as NASH.

Hepatic steatosis is the basic process of NAFLD from early stages to advanced NASH. Increased hepatic fat leads to the induction of cellular stress and inflammation, which results in the activation of various pathways. Oxidative stress is implicated in the induction inflammation, and reactive oxygen species (ROS) generation, which are generated during free fatty acid (FFA) metabolism in microsomes, peroxisomes and mitochondria (Pessayre, 2007). NAFLD related risk factors are widely linked by obesity, insulin resistance (IR), diabetes, dyslipidemia, hypercholesterolemia and proinflammatory state (Eckel et al., 2005; Alberti et al., 2009). There is a close relationship between NAFLD and diabetes onsets since upon IR development inhibition of lipolysis by insulin is repressed in the adipose tissue. Following, the release of FFAs from adipose tissue to the blood increases and, in turn, contributes to IR. As a result, accumulation of FFAs will cause induction of oxidative stress and hepatocellular damage (Day, 2010).

Recently, ER stress has been implicated to be a sensor of cellular stress and reduced ER stress response in NAFLD suggests its role both in the development of steatosis and in the progression of the disease. ER restores cellular homeostasis since it handles accumulation of misfolded proteins either by directing the proteins to refolding or to degradation mechanisms (Tsai and Weissman, 2010). However, in several diseases such as NASH, increased demand of protein synthesis leads to disruption of ER homeostasis and ER stress results in lipid biosynthesis, insulin action, inflammation, and apoptosis (Kim et al., 2008; Hotamisligil, 2010). In this direction, it is important to understand the mechanisms that disrupt ER homeostasis and the role of ER-mediated signaling in NASH.

Meanwhile, oxidative and ER stress play a major role in the aging process. Aging is associated with an increase in lipid accumulation in liver, which is a key pathology of NAFLD. In connection with this information, studies have shown several age-related hepatic changes such as increased hepatocyte size and binucleated cells and reduction in mitochondrial number which affect liver morphology, physiology, and oxidative capacity (Premoli et al., 2009). Therefore, the risk for NAFLD increases with age and NAFLD is likely to be regarded as an age-related liver disease also regarding the role of ER stress in NAFLD progression.

On the other hand, more recently, microRNAs (miRNAs, miRs) have been suggested to have an important role in NAFLD pathogenesis. miRNAs are small, noncoding RNAs that regulate gene expressions and crucial cellular processes (Carthew and Sontheimer, 2009). The data obtained from studies have demonstrated that altered miRNA expressions are related with cell growth, apoptosis, and inflammation as well as with several pathological conditions including NAFLD (Sayed and Abdellatif, 2011). Therefore, studies that are focused on the role of miRNAs in the pathogenesis of NAFLD are increasing and their potential to be used as therapeutic targets is gaining interest. Recent studies have also revealed a close relation between ER stress responses and miRNAs (Bartoszewski et al., 2011). Although this relationship of ER stress and miRNAs has not been fully elucidated, it seems to be acting in a bidirectional way. Regarding its importance, the role of ER stress related molecular mechanisms in NASH pathogenesis, and how miRNAs contribute to disease progression under ER stress conditions are discussed in this review.

2. Cholesterol and lipid metabolism in NASH

Cholesterol, operates many important functions in the body and it is synthesized *de novo* by extrahepatic tissues and the liver itself. The synthesis of cholesterol occurs in the ER and is strictly regulated by the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCoAR), which catalyzes the first reaction of cholesterol biosynthesis (Cohen and Fisher, 2013). The uptake of cholesterol from lipoproteins occurs through different surface proteins, including the low-density lipoprotein (LDL) receptor (LDLR) and the scavenger receptor class B type I (SR-BI) (Cohen and Fisher, 2013; Cortes et al., 2014). Cholesterol metabolism is highly regulated by metabolic and trafficking pathways. These pathways involve multiple metabolic and transport-related genes whose expressions are regulated by several transcription factors, including the Sterol regulatory element-binding protein 2 (SREBP-2), Liver X receptor alpha (LXR-alpha) and Farnesoid X receptor (FXR) (Luu et al., 2013; Kalaany and Mangelsdorf, 2006). Cholesterol-related metabolic pathways in hepatocytes include *de novo* cholesterol synthesis with acetyl-CoA mevalonate-cholesterol pathway, cholesterol intake via LDL and chylomicron residues, cholesterol secretion into the blood by very low-density lipoprotein (VLDL), cholesterol secretion and intake through ATP Binding Cassette G5/G8 (ABCG5/G8), ABCA1 and Niemann-Pick C1-Like 1 (NPC1L1).

In healthy hepatocytes, these pathways cooperate with each other to keep cholesterol levels in normal range. However, cholesterol related pathways are highly damaged in NAFLD patients (Table 1). Since cholesterol is an important factor for the membrane bilayer permeability and fluidity, altered cholesterol metabolism