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Review

Cholesterol and bile acid-mediated regulation of autophagy in fatty liver diseases and atherosclerosis

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ABSTRACT

Liver is the major organ that regulates whole body cholesterol metabolism. Disrupted hepatic cholesterol homeostasis contributes to the pathogenesis of nonalcoholic steatohepatitis, dyslipidemia, atherosclerosis, and cardiovascular diseases. Hepatic bile acid synthesis is the major catabolic mechanism for cholesterol elimination from the body. Furthermore, bile acids are signaling molecules that regulate liver metabolism and inflammation. Autophagy is a highly-conserved lysosomal degradation mechanism, which plays an essential role in maintaining cellular integrity and energy homeostasis. In this review, we discuss emerging evidence linking hepatic cholesterol and bile acid metabolism to cellular autophagy activity in hepatocytes and macrophages, and how these interactions may be implicated in the pathogenesis and treatment of fatty liver disease and atherosclerosis.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease in the Western countries, and it is more common in the obese and type-2 diabetic population [1]. Simple steatosis usually does not require treatment, while some NAFLD patients may progress to nonalcoholic steatohepatitis (NASH). NASH is a debilitating form of NAFLD characterized by hepatocellular injury, chronic inflammation, and a higher risk of end stage liver diseases such as cirrhosis and liver cancer [1]. The mechanisms underlying NASH pathogenesis are still incompletely understood. The role of free fatty acids in causing lipotoxic liver injury in NASH has been extensively studied [2]. Emerging evidence supports that cellular non-esterified free cholesterol (FC) accumulation contributes significantly to hepatocyte injury and inflammation in NASH [3,4]. Indeed, FC accumulated at significantly higher levels in NASH livers than in normal livers and simple steatotic liver in humans [5]. FC accumulation in hepatocytes causes mitochondrial dysfunction, which sensitizes hepatocytes to cytokine and stress-induced cell death [3]. In addition, cholesterol-laden foamy Kupffer cells were found at early stage of NASH and showed pro-inflammatory phenotypes [6], suggesting cholesterol accumulation triggers macrophage activation in NASH. Disrupted hepatic cholesterol homeostasis is also a major cause of hyperlipidemia. Intracellular lipid accumulation is a driver of hepatic secretion of very low density lipoprotein (VLDL), which is the precursor of cholesterol-rich low density lipoprotein (LDL). Elevated circulating VLDL and LDL concentration is a major contributor to the development of atherosclerosis and higher risk of cardiovascular disease (CVD) [7]. Indeed, CVD is the leading cause of mortality in patients with NASH and type-2 diabetes [7]. Therapeutic interventions that improve hepatic cholesterol homeostasis are expected to ameliorate both hepatic and cardiovascular-related complications in NASH and type-2 diabetes.

Autophagy is a highly-conserved lysosomal degradation mechanism, which plays an essential role in maintaining cellular integrity by eliminating protein aggregates and damaged or excessive organelles in mammalian cells [8]. Autophagy is also a catabolic process used by cells to generate nutrients and energy by degrading macromolecules in response to nutrient deprivation [8]. The process of autophagy initiates

Abbreviations: NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; FC, free cholesterol; VLDL, very low density lipoprotein; LDL, low density lipoprotein; mTOR, mechanistic target of rapamycin signaling; AMPK, AMP-activated protein kinase; TG, triglycerides; CE, cholesterol ester; SREBP-2, sterol regulatory element-binding protein-2; ER, endoplasmic reticulum; SCAP, sterol-sensing SREBP cleavage-activating protein; Insig, insulin-induced genes; HMGCR, 3-hydroxy-3-methylglutaryl coenzyme A reductase; LDLR, low density lipoprotein receptor; CYP7A1, cholesterol 7α-hydroxylase; BSEP, bile salt export pump; ABCG5, ATP binding cassette transporter G5; ASBT, apical sodium-dependent bile acid transporter; FXR, farnesoid x receptor; SHP, small heterodimer partner; FGF15, fibroblast growth factor 15; FGF19, fibroblast growth factor 19; FGFR4, FGF receptor 4; NPC1L1, Niemann-Pick-type C1-like1; ACAT, acyl-coA: cholesterol acyltransferase; NPC, Niemann-Pick disease, type C; ASMase, acid sphingomyelinase; LC3, microtubule-associated protein 1 light chain 3; CESD, cholesterol ester storage disease; ApoB100, apolipoprotein B100; LAL, lysosomal acid lipase; n-3 PUFA, n-3 polyunsaturated fatty acids; oxLDL, oxidized LDL; ApoA-I, apolipoprotein A-I; HDL, high density lipoprotein; RCT, reverse cholesterol transport; ABCA1, ATP binding cassette transporter A1; ABCG1, ATP-binding cassette transport G1; LXR, liver X receptor; TFEB, transcriptional factor EB; S1PR2, sphingosine-1-phosphate receptor 2

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from the formation of a double membrane vesicle called autophagosome, which may sequester protein aggregates, intracellular organelles, lipids, etc. Autophagosomes then fuse with lysosomes to form autolysosomes where the autophagy cargos are degraded by lysosomal enzymes and released into the cytosol for various utilizations. Autophagy is a highly complex cellular process regulated by diverse cellular signaling pathways, among which the mechanistic target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK) reciprocally regulate autophagy activity in response to changes of cellular nutrient abundance, stress, growth factor stimuli, etc. [8]. Lipophagy is a type of autophagy that transports intracellular triglycerides (TG) and cholesterol esters (CE) stored in the lipid droplets to the lysosomes to be hydrolyzed, and thus controls cellular lipid mobilization and energy homeostasis [9]. Furthermore, the complex interactions among overnutrition, defective autophagy and inflammation are thought to play important roles in the pathogenesis of fatty liver diseases [9–13] and atherosclerosis [14–16]. In this concise review, we will mainly focus on recent findings on cholesterol and bile acid-mediated regulation of autophagy in hepatocytes and macrophages and the relevant implications in the pathogenesis and treatment of fatty liver disease and atherosclerosis.

2. Regulation of hepatic cholesterol and bile acid homeostasis

The liver plays a central role in regulating whole body cholesterol homeostasis. Hepatocytes maintain cellular cholesterol homeostasis by coordinately controlling several cholesterol input and elimination pathways (Fig. 1). Hepatocytes acquire cholesterol primarily via de novo synthesis and receptor-mediated lipoprotein uptake from the circulation. These input pathways are mainly regulated by the sterol regulatory element-binding protein-2 (SREBP-2)-mediated cholesterol sensing mechanism [17]. SREBP-2 is synthesized as a precursor protein retained in the endoplasmic reticulum (ER) membrane and associated with the sterol-sensing SREBP cleavage-activating protein (SCAP). When cellular cholesterol level is high, cholesterol binding to SCAP causes a conformational change that induces SCAP interaction with the ER membrane protein insulin-induced genes (Insigs), which retains the SREBP-2-SCAP complex in the ER. A decrease of cellular cholesterol promotes SREBP-2-SCAP complex translocation to the Golgi where proteolytic cleavage of SREBP-2 occurs. The released truncated and mature SREBP-2 enters the nucleus to induce a large set of cholesterol synthesis and transport genes including 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) and low density lipoprotein receptor (LDLR). Activation of these genes raises intracellular cholesterol levels, which in turn inhibits SREBP-2 cleavage activation via a negative feedback loop [17].

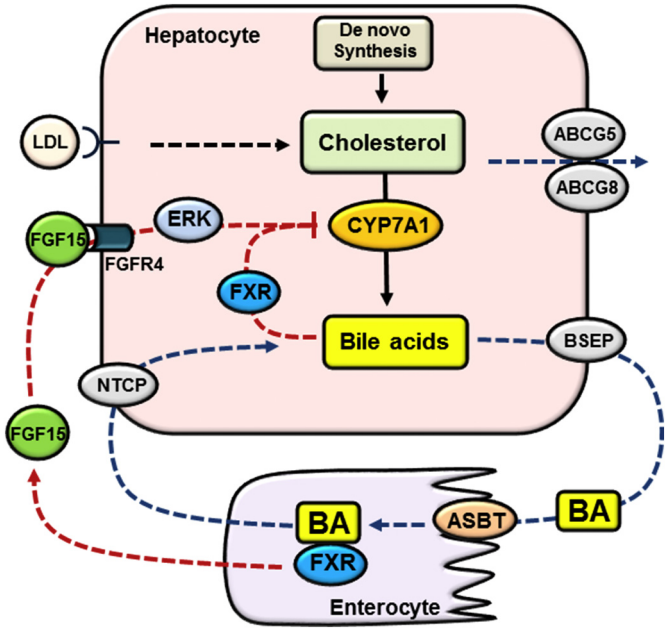

Fig. 1. Bile acid synthesis and enterohepatic circulation. Hepatocytes acquire cholesterol via de novo synthesis and receptor-mediated endocytosis of cholesterol-rich lipoproteins. Hepatocytes eliminate cholesterol via bile acid synthesis and biliary secretion of cholesterol via ABCG5/ABCG8. Bile acids are synthesized from cholesterol in hepatocytes. CYP7A1 catalyzes the first and rate-limiting step in cholesterol conversion into bile acids. Bile acids are secreted into the bile via BSEP and subsequently released into the small intestine. The majority of bile acids is re-absorbed into the enterocytes via ASBT and transported back to the liver via portal circulation. Basolateral NTCP transports conjugated bile acids into the hepatocytes. Bile acids in the hepatocytes activate FXR to inhibit CYP7A1. Bile acids in the small intestine activate FXR to induce FGF15, which binds and activates FGFR4 to inhibit CYP7A1 partially via ERK signaling.

Hepatocytes eliminate the majority of cholesterol from the body by converting cholesterol into bile acids and secreting cholesterol into the bile (Fig. 1) [18]. Bile acid synthesis occurs exclusively in hepatocytes and is the only quantitatively significant cholesterol catabolic mechanism. The ER resident cytochrome *p*-450 enzyme cholesterol 7α-hydroxylase (CYP7A1) catalyzes the first and rate-limiting step in the conversion of cholesterol into bile acids [18]. Bile acids are secreted into the bile via the bile salt export pump (BSEP) [19], while cholesterol is secreted into the bile by the ATP binding cassette transporter G5 (ABCG5) and ABCG8 functional heterodimer on the canalicular side of the hepatocytes [20]. Biliary bile acid secretion generates bile flow and helps solubilize cholesterol in the bile by forming micelles. Once released into the small intestine after a meal, bile acids help emulsify dietary fat and facilitate intestine absorption of lipid and fat-soluble vitamins. It is estimated that over 95% of the bile acids is re-absorbed via the apical sodium-dependent bile acid transporter (ASBT) mainly in the terminal ileum and transported back to the liver for re-secretion into the bile. The transport of bile acids between the liver and the intestine is a process termed the enterohepatic circulation of bile acids. The significant intestinal bile acid conservation means that the liver needs to synthesize a small fraction of the total bile acid pool to compensate for the daily fecal loss of bile acids in order to maintain a constant bile acid pool over time.

Under normal physiology, bile acid homeostasis is mainly achieved through bile acid-mediated feedback inhibition of hepatic bile acid synthesis (Fig. 1) [18]. Bile acids are endogenous ligands for the nuclear receptor farnesoid x receptor (FXR) [21,22]. FXR is highly expressed in the hepatocytes and enterocytes that are routinely exposed to high concentrations of bile acids. The bile acid-sensing FXR exerts a tight control of the hepatic bile acid synthesis rate by inhibiting the transcription of the *CYP7A1* gene via several redundant mechanisms [23]. In hepatocytes, FXR induces a repressor small heterodimer partner (SHP) to inhibit the *CYP7A1* gene transcription [24]. More recently, a posttranscriptional mechanism has been reported whereby FXR induces a RNA-binding protein ZFP36L1 to decrease the stability of CYP7A1 mRNA [25]. The small intestine is a major reservoir of the bile acid pool. Intestinal FXR senses elevated bile acids to transcriptionally induce mouse fibroblast growth factor 15 (FGF15), which acts as an endocrine hormone to inhibit the hepatic *CYP7A1* gene transcription [26]. In the enterohepatic system, FGF15 is highly expressed in the terminal ileum but not expressed in mouse hepatocytes [26]. Fibroblast growth factor 19 (FGF19) is the human ortholog of the mouse FGF15. FGF19 is expressed in both the hepatocytes and the enterocytes and its transcription is induced by bile acids and FXR in both types of cells [27]. FGF15 and FGF19 bind the cell surface receptor FGF receptor 4 (FGFR4) in hepatocytes to inhibit the *CYP7A1* gene via ERK1/2-dependent mechanisms. The downstream targets mediating this inhibition remain to be determined.