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REVIEW

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The roles of nuclear receptors in cholesterol metabolism and reverse cholesterol transport in nonalcoholic fatty liver disease

Zhichi Li | **Dantong Zheng** | **Tiantian Zhang** | **Shan Ruan** | **Na Li** | **Yang Yu** | **Yang Peng** | **Difei Wang**

Shengjing Hospital of China Medical University, Gerontology, and Geriatrics, Liaoning, China.

Correspondence
Yang Peng, Shengjing Hospital of China Medical University, Gerontology, and Geriatrics, Liaoning, China.
Email: pengy@sj-hospital.org

Difei Wang, Shengjing Hospital of China Medical University, Gerontology, and Geriatrics, Liaoning, China.
Email: dfwang@cmu.edu.cn

Abstract

As the most prevalent chronic liver disease globally, NAFLD encompasses a pathological process that ranges from simple steatosis to NASH, fibrosis, cirrhosis, and HCC, closely associated with numerous extrahepatic diseases. While the initial etiology was believed to be hepatocyte injury caused by lipid toxicity from accumulated triglycerides, recent studies suggest that an imbalance of cholesterol homeostasis is of greater significance. The role of nuclear receptors in regulating liver cholesterol homeostasis has been demonstrated to be crucial. This review summarizes the roles and regulatory mechanisms of nuclear receptors in the 3 main aspects of cholesterol production, excretion, and storage in the liver, as well as their cross talk in reverse cholesterol transport. It is hoped that this review will offer new insights and theoretical foundations for the study of the pathogenesis and progression of NAFLD and provide new research directions for extrahepatic diseases associated with NAFLD.

INTRODUCTION

NAFLD is a prevalent chronic liver disease affecting approximately 2 billion people worldwide.[1] The condition is defined by the presence of fatty degeneration in $>5\%$ of liver cells, often coupled with metabolic risk factors, such as obesity and type 2 diabetes, and a lack of excessive alcohol consumption (≥ 30 g/d for men, ≥ 20 g/d for women) or other chronic liver diseases.[2] The disease can progress from simple hepatic steatosis to NASH, then to advanced liver fibrosis, cirrhosis, or HCC. Over the past 20 years, the burden of NAFLD in China has increased significantly; the prevalence began to increase from 23.8% in the early- to mid-2000s, accelerating in 2010, then reaching 32.9% in 2018, resulting in an average prevalence of 29.6%.[3]

Abbreviations: ABCA1, ATP-binding cassette transporter A1; ABCG5, ATP-binding cassette transporter G5; ACAT, acyl-CoA cholesterol acyltransferase; AMPK, AMP-activated protein kinase; apoA-I, apolipoprotein AI; CETP, cholesteryl ester transfer protein; CtBP, C-terminal binding protein; CYP7A1, cytochrome P450; FGFR4, fibroblast growth factor receptor 4; FXR, farnesoid X receptor; GR, Glucocorticoid receptor; HFD, high-fat diet; HNF4α, hepatocyte nuclear factor 4 alpha; LXR, liver X receptor; NRs, nuclear receptors; NZO, New Zealand Obese mice; PPAR, peroxisome proliferator-activated receptor; PPRE, peroxisome proliferator response element; RA, Retinoic acid; RCT, reverse cholesterol transport; RXR, retinoid X receptor; SHP, small heterodimer partner; SR-B1, scavenger receptor B1; TCHO, total cholesterol; TG, Triglyceride.

An increase in NAFLD prevalence is associated globally with aging, obesity, and diabetes,[4] whereas in China, it is associated with an increase in older and young patients exhibiting changes in diet and lifestyle. From 2010 to 2018, the incidence of NAFLD in Chinese people aged below 60 years was higher than that in those aged above 60 years.[3]

Patients with NAFLD commonly exhibit a series of complex metabolic dysfunctions, including insulin resistance, lipid metabolism abnormalities, gut microbiota disturbances, and abnormal uric acid metabolism. Additionally, NAFLD is positively correlated with the onset of atherosclerotic diseases, thereby increasing the risk of stroke and myocardial infarction, which can lead to systemic functional impairments or even death.[5] Moreover, the increasing prevalence of NAFLD among young populations may exacerbate its burden on society. Therefore, it is imperative to further elucidate the pathogenesis of NAFLD. This review summarizes the existing literature on NAFLD pathogenesis, specifically, the roles and regulatory mechanisms of nuclear receptors (NRs) in (1) maintaining hepatic cholesterol homeostasis, (2) the development and progression of NAFLD, and (3) cross talk during reverse cholesterol transport (RCT).

NAFLD PATHOGENESIS

The primary driving factor of NAFLD is nutrient excess, which leads to the excessive accumulation of liver lipids and disrupts the balance of hepatic lipid metabolism.[6] However, research increasingly suggests that triglycerides, which are lipid storage substances, serve as a buffer against lipid-induced liver damage,[7,8] whereas the accumulation of free fatty acids,[9] cholesterol,[10] phosphatidylcholine,[11] and ceramides[12] plays a more critical role in the development and progression of NAFLD. Among these factors, maintaining cholesterol metabolic homeostasis is particularly crucial.[10]

Cholesterol homeostasis

Cholesterol is a precursor for the synthesis of bile acids, vitamins, and steroid hormones and is an essential lipid molecule in animal cells. Cholesterol is crucial not only for maintaining the barrier function and fluidity of cell membranes but also for playing an important role in intercellular signaling through the formation of lipid rafts on the cell membrane.[13] Therefore, maintaining cholesterol homeostasis is essential for maintaining basic body activities.

Cholesterol homeostasis refers to the dynamic balance between the production, excretion, and storage of cholesterol. Endogenous cholesterol is synthesized from acetyl-CoA through a series of >30 reactions involving over 20 enzymes. Conversely, exogenous cholesterol from food is absorbed by the intestines and transported to the liver via chylomicrons. The liver, as the central hub of cholesterol metabolism, converts both endogenous and exogenous cholesterol into VLDL and releases it into the bloodstream. VLDL is then processed into LDL, which is recognized by LDL receptors on the cell surface and internalized, allowing the cholesterol to be utilized by cells. Excess cholesterol is either esterified by acyl-CoA cholesterol acyltransferase (ACAT) and stored in lipid droplets or incorporated into plasma lipoproteins and released into the bloodstream. Cholesterol in the liver cells can also be excreted through the intestines by being converted into bile acids in the gallbladder. Excess cholesterol intake or synthesis can lead to cholesterol accumulation in the liver and bloodstream, resulting in pathological changes in organs, such as fatty liver and atherosclerosis. Furthermore, mutations in the genes regulating cholesterol homeostasis can lead to a range of inherited diseases, including Schnyder corneal dystrophy,[14] Smith-Lemli-Opitz syndrome,[15] familial hypercholesterolemia,[16] Tangier disease,[17] and sitosterolemia.[18] Acquired imbalances in cholesterol homeostasis can also lead to several diseases, such as Parkinson disease,[19] Alzheimer disease,[20] muscular dystrophy,[21] cancer,[22–24] and common atherosclerosis-related conditions.[25,26]

As the central of cholesterol metabolism in the body, the liver plays a crucial role in cholesterol homeostasis; approximately 50% of cholesterol is produced by the liver.[27] The liver also utilizes the scavenger receptor B1 (SR-B1) pathway to clear circulating cholesterol carried by HDL and maintain peripheral cholesterol homeostasis.[28] Approximately 70% of retinoic acid in the human body is stored in HSCs, which play a critical role in the progression of NAFLD to liver fibrosis and cirrhosis.[29] The liver is the only organ that can eliminate excess cholesterol by converting it into bile acids and excreting it with bile.[30] Given the liver's crucial role in the development, progression, and treatment prognosis of NAFLD, the regulation of cholesterol homeostasis has become a topic of interest in recent years. Studies have demonstrated the important role of NRs in regulating and stabilizing hepatic lipid metabolism[31–37] (Fig. 1).

Role of cholesterol in NAFLD

The accumulation of liver cholesterol is caused by an increase in endogenous cholesterol synthesis and increased absorption of intestinal cholesterol, as well as obstructed excretion of free cholesterol in bile, conversion of bile acids, and nonbiliary transintestinal cholesterol efflux.[38] In addition, animal models fed with a high-cholesterol diet exhibit NAFLD characteristics and are more likely to develop liver fibrosis and atherosclerosis manifestations than models fed with a high-fat diet alone.[39] Severe liver fibrosis and cirrhosis are known risk factors for the development of liver

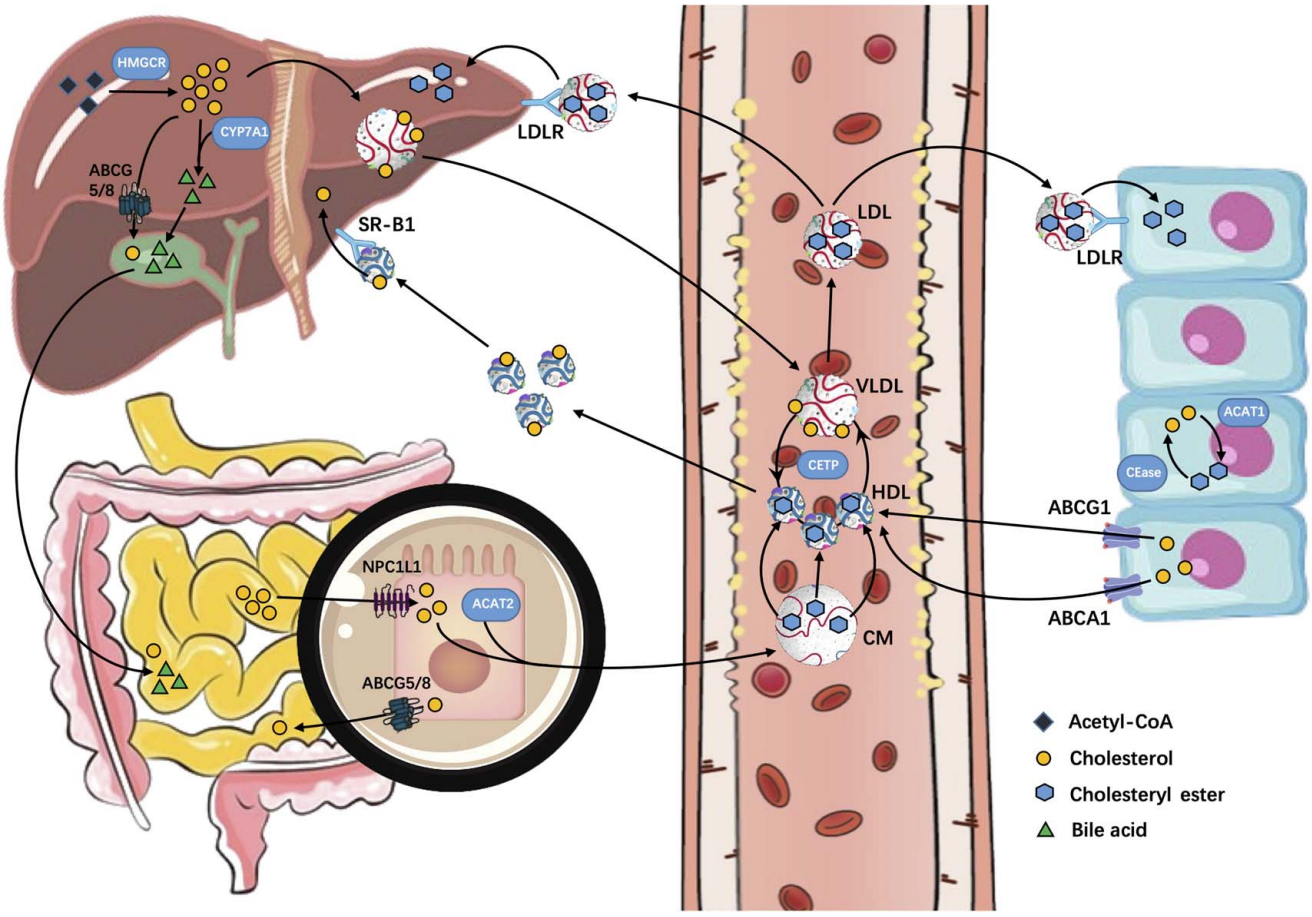

FIGURE 1 The process of cholesterol from synthesis, absorption, utilization, and excretion. Abbreviations: ABCA1, ATP-binding cassette transporter A1; ABCG5, ATP-binding cassette transporter G5; CYP7A1, cytochrome P450; LDLR, LDL receptor; SR-B1, scavenger receptor B1.

cancer, which is the third deadliest cancer worldwide.[40] Indeed, a significant proportion of liver cancer is caused by NAFLD, which is more hazardous because of the high incidence, late diagnosis, and poor prognosis of HCC induced by this type of NAFLD than HCC induced by viral hepatitis.[41,42] A large body of research has shown that free cholesterol in the liver is a key pathogenic factor in promoting HCC.[43–45] Overall, cholesterol plays a crucial role in the occurrence of NAFLD and the development of liver cirrhosis, HCC, and extrahepatic atherosclerotic diseases.

NUCLEAR RECEPTORS

NRs are among the most abundant transcriptional regulatory factors in metazoans and play crucial roles in metabolism, sex determination, reproductive development, and maintaining homeostasis.[46–48] The human genome contains 48 NRs, in contrast to the 49 NRs found in rodents.[49] NRs comprise an N-terminal regulatory region that activates transcription, DNA-binding domains containing 2 zinc finger structures, a nonconserved hinge region, a ligand-binding domain, and a variable C-terminal region.[50] NRs can be divided into 7 subfamilies, ranging from NR0 to NR6.[51]

As the ligands for many NRs are fatty acids, steroids, and oxysterols, their role in liver lipid metabolism has received extensive attention.[36,37,52–54] Table 1 lists the NRs involved in cholesterol metabolism and NAFLD. In the following sections, we summarize the roles of several NRs in maintaining hepatic cholesterol homeostasis and in the development and progression of NAFLD.

Liver X receptor

As a cholesterol sensor, liver X receptor (LXR) activates the expression of a series of genes related to cholesterol absorption, efflux, transport, and excretion under increased cellular cholesterol levels.[126] LXR has 2 homologous subtypes, LXRα and LXRβ, which have different tissue distributions. LXRα is highly expressed in metabolically active tissues and cell types, including liver, intestine, adipose tissue, and macrophages, whereas LXRβ is more widely expressed. Its physiological ligands include oxysterols, including 24(S), 25-epoxycholesterol, 25-hydroxycholesterol, and 22(R)-hydroxycholesterol,

TABLE 1 The role of nuclear receptors in hepatic cholesterol metabolism and NAFLD

Gene name	Nuclear receptor	Ligand	Function in cholesterol metabolism and NAFLD	References
NR0B1	DAX1	Orphan	DAX-1 inhibits the transcriptional activity of LRH-1 and LXRα, and inhibits gluconeogenesis by negatively regulating HNF4A	[55–57]
NR0B2	SHP	Orphan	The expression of SHP inhibits CYP7A1, and downregulation of SHP accelerates the transformation of cholesterol to bile acids by activating CPY7A1	[58,59]
NR1A1	TRα	Thyroid hormones	Downregulation of TRα alleviates diet-induced hepatic steatosis	[60,61]
NR1A2	TRβ	Thyroid hormones	Loss of TRβ shows excessive lipid accumulation in both human and mouse livers	[62–64]
NR1B1	RARα	Retinoic acids	Loss of RARα-induced hepatic steatosis and decreased macrophage cholesterol effection in HFD-fed mice. Upregulation of RARα could reduce hepatic lipid accumulation by decreasing CD36 expression	[65–67]
NR1B2	RARβ	Retinoic acids	Upregulation of RARβ can alleviate hepatic lipid accumulation in hepatocytes	[68,69]
NR1B3	RARγ	Retinoic acids	Upregulation of RARγ activates ABCA1-mediated cholesterol efflux	[70]
NR1C1	PPARα	Fatty acids	Metabolomics has revealed that PPARα is an important regulator of bile acids by interacting with SREBP2, and that PPAR-α/γ agonist Saroglitazar significantly improves insulin resistance and dyslipidemia in NAFLD	[71–73]
NR1C2	PPARβ	Fatty acids	PPARβ/δ inhibits CYP7a1 expression by upregulating FGF21	[74]
NR1C3	PPARγ	Fatty acids	PARγ inhibitor GW9662 can reduce the development of NAFLD by inhibiting TLR4, but PPARγ can promote cholesterol effluence by inducing the expression of ABCA1 in gallbladder epithelium	[75,76]
NR1D1	REV-ERBα	Heme	REV-ERB coordinates the regulation of most genes encoding important enzymes in the cholesterol biosynthesis pathway, and downregulation of Rev-ERbα promotes bile acid metabolism through upregulation of CYP7A1	[77–79]
NR1D2	REV-ERBβ	Heme	Activation of REV-ERBα/β reduces hepatic triglyceride storage and inhibits cholesterol synthesis, and can increase promoter activity of CYP7A1	[80,81]
NR1F1	RORα	Sterols	Overexpression of RORα reduces diet-induced hepatic lipid accumulation, and its inverse agonist SR1001 regulates intestinal excretion of cholesterol by upregulating ABCG5/G8	[82,83]
NR1F3	RORγ	Sterols	Knockout of RORγ may reduce bile acid synthesis by decreasing levels of Cyp8b1, Cyp7b1, and Cyp27a1	[84]
NR1H4	FXRα	Bile acids	FXRα can promote CYP7A1 expression through FGF19 and SHP/LRH-1 pathway, competitively inhibit LXRα to promote CETP transcription and reduce liver cholesterol uptake and accumulation	[85–87]
NR1H3	LXRα	Oxysterols	LXRα activates ABCG5/8 to promote the excretion of cholesterol in bile. LXRα can promote cholesterol effection in gallbladder epithelium by inducing the expression of ABCA1. LXRα deficiency leads to downregulation of CYP7A1 level, leading to liver cholesterol accumulation	[76,88,89]
NR1H2	LXRβ	Oxysterols	LXRβ agonists induce the expression of cholesterol pump ABCA1 in bile duct cells and promote the output of cholesterol from the basolateral membrane of bile duct cells	[90]

NR1I1	VDR	1α,25-dihydroxyvitamin D3	VDR is significantly highly expressed in NAFLD, and its deficiency leads to reduced fat accumulation when aging and adult mice are fed a high-fat diet	[91,92]
NR1I2	PXR	Endobiotics and xenobiotics	PXR aggravated hepatic steatosis caused by a high-fat diet, and PXR KO mice had significantly reduced levels of liver triglycerides, hepatic steatosis, serum total bile acids, and liver gene expression of enzymes involved in the bile acid synthesis pathway	[93,94]
NR1I3	CAR	Xenobiotics	CAR is able to confer hepatoprotection from bile acids by increasing their sulfation and excretion	[95,96]
NR2A1	HNF4α	Fatty acids	Loss of HNF4α enhances hepatic cholesterol accumulation by inhibiting CYP7A1/CYP8B1, FXR, and ABCAS1, and loss of HNF4α in mice shows hepatic steatosis and reduced plasma cholesterol levels	[97–99]
NR2B1	RXRα	9-*Cis* retinoic acid	RXRα serves as a heterodimerization partner for PPARα, PXR, LXR, and FXR to participate in the regulation of cholesterol metabolism	[100–104]
NR2C2	TR4	Orphan	TR4 knockout reduces liver lipid accumulation and can reduce apoE levels	[105,106]
NR2E1	TLX	Orphan	Mice with NR2E1 knocked out display a significant hepatic steatosis phenotype	[107]
NR2F1	COUP-TFα	Orphan	COUP-TFα exerts a transcriptional repression effect by binding to the promoter region of apoCIII	[108]
NR2F2	COUP-TFβ	Orphan	HNF4 and coup-TF-β synergistically activate the transcription of the CYP7A1 promoter	[109,110]
NR2F6	EAR2	Orphan	EAR2 inhibits the transcription of the genes encoding apoB, apoCIII, and apoAII	[111]
NR3A1	ERα	Estrogens	ERα upregulates the expression of intestinal Npc1l1, Abcg5 and Abcg8, inhibits the transcriptional activity of LXRα in liver, and interacts with FXR in an estradiol-dependent manner to inhibit its function in vitro	[112–114]
NR3A2	ERβ	Estrogens	Absence of Erβ alleviates the disruption of bile acid and cholesterol metabolism induced by perfluorooctane sulfonate	[115]
NR3B1	ERRα	Orphan	VLDL-TG secretion is reduced in ERRα KO mice, leading to hepatic steatosis	[116]
NR3B3	ERRγ	Orphan	Overexpression of ERRγ upregulates the expression of CYP7A1 both *in vitro* and *in vivo*	[117]
NR3C1	GR	Glucocorticoids	GR interacts with FXR to reduce FXR transcriptional activity and promote hepatic cholestasis in mice by recruiting CtBP coblocking complex, and GR regulator CORT118335 can reverse hepatic cholesterol accumulation	[118,119]
NR3C2	MR	Mineralocorticoids and glucocorticoids	Specific blockade of MR exhibits hepatic antisteatotic effects	[120]
NR3C4	AR	Androgens	AR reduces cholesterol synthesis by mediating phosphorylation of HMGCR and promotes cholesterol synthesis and accumulation by activating sterol-regulatory element-binding protein isoform 2	[121,122]
NR4A1	Nur77	Orphan	Nur77 regulates liver lipid metabolism by inhibiting SREBP1c activity, and the levels of TCHO, LDLR, HMGCR, and Nur77 in HepG2 cells are negatively correlated	[123,124]
NR5A2	LRH-1	Phospholipids	LRH-1 regulates hepatic cholesterol excretion through CYP7A1 and CYP8B1	[125]

Abbreviations: ABCA1, ATP-binding cassette transporter A1; CYP7A1, cytochrome P450; FXR, farnesoid X receptor; HNF4α, hepatocyte nuclear factor 4 alpha; KO, knockout; LDLR, LDL receptor; LXR, liver X receptor; PPAR, peroxisome proliferator-activated receptor; SHP, small heterodimer partner.

which are metabolites of cholesterol.[127] Previous studies have shown that high-cholesterol diets result in significantly more cholesterol accumulation in the livers of LXRα-knockout mice than in those of wild-type mice.[128]

NPC1L1 is expressed in the brush border membrane of intestinal cells and is essential for intestinal cholesterol absorption.[129] Treatment of Caco-2 cells with the LXR agonists T0901317 and GW3965 results in a significant decrease in hNPC1L1 mRNA levels,[130] indicating that LXR activation can inhibit cholesterol absorption via dietary intake. SREBP2 regulates cellular cholesterol levels at the transcriptional level[131]; in the liver of LXR (−/−) mice fed a low-cholesterol diet, the mRNA levels of cholesterol synthesis-related genes comprising SREBP-2 were significantly higher than those in wild-type mice,[128] further demonstrating the crucial role of LXR in maintaining cholesterol uptake and synthesis.

Cytochrome P450 (CYP7A1) is the rate-limiting enzyme in bile acid synthesis. Binding of LXRα to the promoter region of CYP7A1 in rodents induces the conversion of excess cholesterol to bile acids,[127] whereas LXRα deficiency in mice leads to cholesterol accumulation in the liver.[128] However, the same phenomenon is not observed because the binding site of LXRα is missing in the human CYP7a1 promoter region.[132,133] ATP-binding cassette transporter A1 (ABCA1) is a crucial mediator for cholesterol efflux from cells to apolipoprotein AI (apoA-I) and the generation of HDL, which transfers peripheral cholesterol to the liver for metabolism to prevent atherosclerotic diseases.[134] The transfection of LXRα and retinoid X receptor (RXR) can transactivate the transcription of ABCA1 in reverse in 293 cells.[135] Moreover, activating the AMPK pathway can upregulate the mRNA and protein levels of LXRα and ABCA1. Additionally, knocking out LXRα can eliminate the upregulation effect of AMPK on ABCA1.[136] Apart from ABCA1, ABCG1 also mediates cholesterol efflux to HDL.[137] Multiple LXR and RXR heterodimer response elements have also been found in the ABCG1 gene.[138] However, the mechanism by which cholesterol efflux is mediated by ABCG1, which is regulated by LXR remains unclear. ATP-binding cassette transporter G5 (ABCG5)/8 is expressed as a heterodimer on the surface of hepatocytes and intestinal cells and mediates cholesterol excretion into bile and the intestines.[139] ABCG5/8 levels are also regulated by LXR.[140] Thus, downregulation of LXR inhibits cholesterol efflux from macrophages, whereas upregulation of LXR increases the levels of ABCG5/8 in the liver and small intestine, promoting cholesterol reverse transport.[141]

The expression of LXR is correlated with the severity of NAFLD,[142–144] with significant cholesterol accumulation observed in LXR-knockout mice fed a high-cholesterol diet.[145] Although some LXR agonists, such as GW6340, 22(R)-hydroxycholesterol, and LXR-623, exhibit well tolerated,[146,147] LXR activation can promote hepatic lipid synthesis and inhibit VLDL degradation[148,149]; thus, it is rarely used for the clinical treatment of NAFLD. Nevertheless, its potential as a drug target is gradually being recognized.

Hepatocyte nuclear factor 4 alpha

Hepatocyte nuclear factor 4 alpha (HNF4α) is a nuclear transcription factor expressed in the liver, kidney, intestine, and pancreas[150]; it binds to DNA as a homodimer and is the main regulatory factor for the expression of bile acid, lipid, glucose, and drug metabolism genes.[36,151] Mutations in the HNF4α gene can cause maturity-onset diabetes of the young in adolescents.[152] HNF4α is critical for pancreatic islet β-cell proliferation, as mice with HNF4α knockout in their β cells cannot respond to insulin resistance-induced proliferation.[153] Mutations in HNF4α are also associated with changes in HDL cholesterol,[154,155] which has prompted suggestions that HNF-4α is a central regulator of glucose and lipid metabolism.[156] Previous animal studies have shown that HNF4α-knockout mice exhibit significant accumulation of liver cholesterol, as well as significant decreases in total cholesterol, HDL cholesterol, and triglyceride levels in serum relative to the control serum, with a significant increase in serum bile acid concentration.[157] These changes in serum lipid profiles may be attributed to liver dysfunction or defects in lipid transport and metabolism.

SR-B1 mediates cholesterol uptake in the liver, and HNF4α can enhance the transcription of SR-B1 mediated by another NR, peroxisome proliferator-activated receptor (PPAR)γ.[158] A decrease in HNF4α levels can inhibit the expression of NPC1L1 in Caco-2 cells and inhibit the uptake of cholesterol by cells.[159] ApoA-1 is the main carrier protein of HDL and exerts atherosclerosis protective properties by participating in the ABCA1 and ABCG1 pathways involved in RCT.[160,161] ApoA-1-defective mice do not form normal HDL particles and cannot effectively transport cholesterol to liver tissue, leading to cardiovascular diseases such as atherosclerosis. HNF4α, PPARα, and LXR participate in the downregulation of human ApoA-I gene expression and ApoA-I protein secretion mediated by TNFα in HepG2 cells.[162] Moreover, HNF4α is an important transcription factor that binds to the CYP7A1 promoter region. Unlike LXR, HNF4α regulation of CYP7A1 levels appears to be bidirectional, with previous results showing that HNF4α inhibits CPY7A1 transcription levels.[163] In another study, bile acid-induced dissociation of the HNF-4α co-activator complex HNF-4/PGC-1α/cAMP response element binding protein also inhibited CYP7A1 transcription.[164] However, in mice with liver-specific knockout/overexpression of HNF4α, reduced de novo synthesis of fat and

cholesterol was detected in the knockout mice, whereas overexpression of Hnf4α significantly induced the expression of genes related to cholesterol absorption, storage, and excretion, such as Mtp, Apob, Cyp7a1, Cyp8b1, Lrp, Ldlr, SR-B1, Acat2, Lcat, Abca1, Abcg5, Abcg8, Apoa1, Apoa2, and Apoc2. In addition, overexpression of Hnf4α showed no significant effect on Srebp-2, Hmgcr, Srebp-1c, or Fas,[97] indicating that HNF4α plays a critical role in cholesterol metabolism but may not affect lipid synthesis, suggesting the potential role of HNF4α as a cholesterol sensor.

The pathogenesis of NAFLD is related to the abnormal concentration, structure, and function of HDL.[165] In a study on HNF4α-knockout mice, the livers were enlarged and showed obvious lipid changes.[166] Furthermore, research indicates that HNF4α is required for the preventive effect of liver cell-activating transcription factor 3 on the formation of NASH.[167] Additionally, HNF4α can prevent the progression of NAFLD to NASH by regulating P53 and bile acid signaling pathways.[98] These findings indicate that HNF4α not only participates in the pathogenesis of NAFLD but also plays an important role in disease progression. Recent research has shown that small molecule-activated RNA can activate HNF4α and significantly lower blood cholesterol and glucose levels.[151] Furthermore, HNF4α mRNA therapy has been shown to restore the metabolic activity of liver cells in mice with liver fibrosis and in vitro human liver cells.[168]

Peroxisome proliferator-activated receptor (PPAR)

The PPAR family members are vertebrate-specific nutrient-sensing NRs. Three members have been identified in this family: PPARα, β/δ, and γ. The expression and function of the 3 subtypes of PPAR are unique, as is their tissue distribution. PPARαPPARα is highly expressed in the liver, skeletal muscle, and brown adipose tissue, whereas PPARγ is mainly expressed in white adipose tissue, and PPARβ/δ is expressed ubiquitously. The function of PPAR is closely related to energy homeostasis and nutrient sensing. The α and β/δ subtypes are involved in energy utilization, whereas γ contributes to energy storage in fat.[32] PPAR acts as a transcription factor in the form of homologous or heterodimer binding to a cis-acting element called a peroxisome proliferator response element (PPRE) of the target gene.[169]

PPARα plays a crucial role in regulating lipid homeostasis by promoting fatty acid oxidation.[170] Recent research on the NZO mouse model, which simulates human metabolic syndrome, has revealed significant changes in the pathways and targets involved in fatty acid metabolism mediated by PPARα, as well as notable changes in cholesterol-related targets.[171] Interestingly, mice with liver-specific inactivation of fatty acid synthase exhibited lower serum and liver cholesterol levels, decreased SREBP-2, increased HMG-CoA, and reduced cholesterol biosynthesis. However, these phenotypes were corrected after the application of PPARα agonists.[172] Bile acids, formed from cholesterol in the liver, represent an important pathway for eliminating cholesterol from the body. Sterol 12α-hydroxylase is a branching enzyme in the bile acid biosynthesis pathway that determines the ratio of cholic acid to chenodeoxycholic acid. Administration of the PPARα agonist WY-14,643 to mice results in a several-fold increase in sterol 12α-hydroxylase mRNA.[173] Several studies have suggested that alterations in small, dense LDL may increase the risk of NAFLD-associated atherosclerosis and cardiovascular disease.[174,175] Pparα agonists fibrate reduce small dense LDL particles and TG to regulate dyslipidemia in atherosclerotic disease.[176] Additionally, PPARα synergizes with LXR to promote cholesterol excretion, with the co-application of PPARα and LXR agonists increasing fecal cholesterol excretion in mice by more than 12 times that observed with a single agonist.[177] Although the primary biological function of PPARα is related to fatty acid metabolism, researchers are increasingly investigating its role in cholesterol homeostasis and have shown that fenofibrate, a PPARα agonist widely used to treat hyperlipidemia, can also be used to treat NAFLD.[178]

Nur77

The gene induced by nerve growth factor B, also known as Nur77, belongs to the NR subfamily 4A and is encoded by the NR4A1 gene. Nur77 is a type of orphan receptor that can function independent of a ligand despite not having a clear endogenous ligand.[179] Structural studies of the ligand-binding domains of all 3 NR4A members have shown that these receptors lack a conventional-sized ligand-binding pocket because of the presence of large hydrophobic amino acid residue side chains.[180–183] Members of the NR4A subfamily bind to DNA as monomers, homodimers, and heterodimers. As monomers of the NR4A subfamily, they bind to NGFI-B response elements; however, as homodimers and heterodimers with other NR4A members, all 3 members of the NR4A subfamily bind to Nur response elements. Nur77 and Nurr1 can also heterodimerize with the retinoid X receptor.[184–188] In terms of function, the NR4A family is closely related to metabolic diseases.[189–191]

Overexpression of Nur77 in mouse livers can reduce the hepatic triglyceride content and lower the expression of Srebp1c, an important regulator of cholesterol metabolism.[123] The levels of genes involved in hepatic cholesterol metabolism, such as LDLR and HMGCoA

reductase, increase as Nur77 expression is downregulated and decrease as Nur77 expression is upregulated.[124] Treatment with Csn-b, which is a Nur77 transcriptional activator, gradually reduces the gene levels of LDLR, ABCG5, SREBP1c, and SREBP2 in mouse livers, while increasing the gene levels of SR-B1 and hepatic lipase. When Nur77 was knocked out, the expression of these genes was downregulated, and the lipid content in mouse liver was reduced by 39.9% after Csn-b treatment.[192] Another study showed that Nur77 reduces the expression of Abcg5 and Abcg8, which are 2 LXR target genes in mice.[123]

Although the overexpression of Nur77 can help the liver to excrete cholesterol and reduce the hepatotoxicity caused by cholesterol, Nur77 is highly expressed in both HCC and cancerous cirrhosis,[193] which suggests its potential role in the progression of NAFLD to HCC.

Farnesoid X receptor

Farnesoid X receptor (FXR) is a bile acid-activated receptor that is mainly expressed in the liver and intestinal tissues and has 2 members in mammals: FXRα and FXRβ.[194] Existing studies have shown that FXR regulates the metabolism of bile acids, carbohydrates, and lipids.[195,196] After activation, FXR and RXR form a heterodimer and induce expression of the small heterodimer partner (SHP) gene, leading to the transcriptional inhibition of the rate-limiting enzyme in bile acid synthesis, 7α-hydroxylase (CYP7A1).[197] FXR also stimulates the synthesis of FGF-19, which inhibits the expression of CYP7A1 and sterol 12α-hydroxylase (CYP8B1) through the fibroblast growth factor receptor 4 (FGFR4) pathway in hepatocytes.[198–200] The FXR/SHP and FXR/FGF19/FGFR4 pathways constitute the main negative regulators of bile acid synthesis. FXR inhibits the uptake of bile acids in the liver by suppressing the expression of sodium taurocholate cotransporting polypeptide via an SHP-dependent mechanism.[201] FXR also upregulates the expression of genes encoding bile salt export pump and multidrug resistance protein 3 and increases the efflux of bile acids from hepatocytes into the canaliculus.[202,203] Moreover, FXR enhances the expression of organic solute transporter α/β, thereby increasing the efflux of bile acids from hepatocytes into the portal vein.[204] In addition, FXR regulates key enzymes involved in bile acid conjugation and detoxification.[202] Overall, FXR is closely related to the entire metabolic process of bile acid synthesis, transport, and reabsorption.[205,206] In both *in vivo* and *in vitro* models of cholestasis in the liver, FXR activation can improve bile stasis, thereby protecting the liver from the high cytotoxicity of bile acids.[207] Furthermore, FXR induces the synthesis of FGF15/19 and upregulates FGF15/19-FGFR4 signaling, which may increase the risk of HCC.[208] According to previous research, FXR activation exhibits potential antitumor activity in colorectal cancer,[209] HCC,[210] and cholangiocarcinoma.[211]

In a multicentre study, FXR activation inhibited cholesterol uptake and conversion to bile acids but also affected cholesterol synthesis and excretion. Furthermore, FXR activation promoted the expression of liver scavenger receptors, thereby enhancing RCT. Moreover, obeticholic acid not only increased LDL but also decreased HDL,[212] which was further supported by the low HDL levels in animals treated with GW4064 and XL335.[213,214] In contrast, FXR antagonists are more beneficial for hypercholesterolemia.[215–217] Thus, more data are required to better understand the potential of selective FXR agonists for modulating the cholesterol levels of humans, as well as the potential of statins for mitigating the associated adverse effects.

RXRα

RXR consists of 3 subtypes: α, β, and γ. The ligand of RXR is 9-cis RA; however, high concentrations of all-trans RA can also activate RXR by conversion to 9-cis RA.[218] Conventional research on NRs has been limited to identifying ligands and determining their biological functions. However, the discovery of RXR and its ability to serve as a heterodimerization partner for other NRs has ushered in a new era of NR research. To date, studies have revealed that RXR can form heterodimers with other NRs[219–221] and also form homodimers.[222] NRs bind to a DNA sequence called hormone response elements, which contain at least 6 core nucleotides—AGGTCA—and can be constructed into various structured motifs.[223] RXR and its dimerization partners recognize hormone response elements on DNA that are spaced 1 to 5 nucleotides apart. The complexity resulting from these various combinations can be partially explained by the tissue-specific expression of NRs.

The 3 subtypes of RXR are widely expressed *in vivo*, with RXRα being the most abundant subtype expressed in the liver.[220] High doses of all-trans RA have been used to treat acne and reportedly cause hyperlipidemia and hepatotoxicity[224]; the mechanism behind this effect may be that all-trans RA inhibits the transcriptional activation of CYP7A1 by the FXR/RXR dimer.[100] The expression of ABCG1 in the liver is closely related to cholesterol efflux to HDL, and as a heterodimerization partner, RXR participates in almost the entire process of cholesterol efflux through ABCG1. Overexpression of LXR/RXR can activate the transcription of ABCG1 in HepG2 cells,[225] and activation of the RXR/RAR dimer can upregulate the expression of the main component of HDL in the liver (apoA-I).[226] Additionally, the RXR agonist LGD1069 can activate the RXR/PPAR pathway to increase HDL cholesterol levels without changing

apoA-I levels in the liver.[227] CYP3A4 catalyzes the 25-hydroxylation of cholesterol, and 25-hydroxycholesterol is metabolized more quickly by CYP7A1 and CYP8B1 than 4β-hydroxycholesterol.[228] Furthermore, CAR/RXR enhances the transcription of CYP3A4 in the form of heterodimers, and interestingly, LXR can inhibit the transcription of PXR-dependent CYP3A4.[229]

The ligand of RXR is a metabolite of vitamin A, and absorption of vitamin A in the human body requires the assistance of intestinal bile acids. Additionally, as RXR can serve as a dimerization partner for several important NRs in bile acid metabolism, RXR links vitamin A and bile acid metabolism.[230] Both *in vivo* and *in vitro* experiments have demonstrated that vitamin A metabolites can directly regulate the expression of bile acid homeostasis-related genes through RXR or RAR and can also regulate gene transcriptional activity through FXR/RXRα. Furthermore, SHP and FGF19/15, 2 pathways that inhibit bile acid synthesis, are also mediated by vitamin A.[100,231,232] Currently, obstacles to the application of vitamin A for NAFLD treatment include uncertainty regarding vitamin A status in the liver and the cell toxicity caused by high vitamin A concentrations. (Fig. 2).

Reverse cholesterol transport

Although the process from NAFLD to HCC and eventual mortality may persist for decades, it is the accompanying atherosclerotic disease of NAFLD that serves as the primary cause of death.[233] The prevailing view is that the hallmarks of atherosclerosis are uncontrolled uptake of oxidized LDL by macrophages, impaired cholesterol efflux, and accumulation of cholesterol esters as cytoplasmic lipid droplets, leading to foam cell formation in the arterial intima. RCT refers to the process by which excess cholesterol is transported from peripheral tissue cells into circulation, metabolized in the liver, and ultimately excreted in feces, which is the main pathway for the liver to clear excess cholesterol in circulation.

Cholesterol efflux from cells to HDL marks the onset of RCT, in which NRs play a crucial role. Macrophages absorb cholesterol from oxidized LDL through CD36 and scavenger receptor A. Internalized oxidized LDL provides PPARγ activation ligands and fatty acids, which induce the expression of CD36.[234] The loss of NCOR1, an NR corepressor, relieves the inhibition of PPARγ on CD36 transcriptional activity, leading to increased foam cell formation.[235] Tamoxifen can relieve PPARγ activation of CD36 transcription.[236] In a previous study, overexpression of Nur77 reduced CD36 and scavenger receptor A levels, inhibiting the process of macrophage differentiation into foam cells.[237] After macrophages take up cholesterol, ACAT1 catalyzes the formation of cholesterol esters to maintain a balance with free cholesterol. The excessive accumulation of cholesterol esters promotes foam cell formation. PPARα is the target of fibrate drugs, whose activation reduces the cholesterol ester content in macrophages but does not downregulate ACAT1 gene expression. Instead, PPARα promotes the entry of ACAT1 substrates, which are long-chain fatty acids, into mitochondria for β-oxidation, reducing the efficiency of cholesterol esterification and thus reducing the ratio of cholesterol esters to free cholesterol.[238] Excess cholesterol in cells is transported out to mature HDL via SR-B1 and ATP-binding cassette protein G1 (ABCG1) and A1 (ABCA1). Over 70% of cholesterol efflux in macrophages is mediated by ABCA1 and ABCG1.[239] As mentioned previously, the transcription of ABCA1 and ABCG1 is regulated by LXR/RXR heterodimers. Subsequent studies have clarified that the ligand activation of PPARγ amplifies the cholesterol clearance mediated by LXR-ABCA1.[240] An investigation of 131 patients with coronary artery disease also revealed that the use of the PPARγ inhibitor GW9662 led to a decrease in LXR-α and ABCA1 levels in the group, accompanied by impaired cholesterol efflux capacity.[241] Cholesterol carried by HDL is eventually taken up by hepatic SR-B1 receptors after circulation and metabolized in the liver, which brings us back to the liver function discussed at the beginning of this review.

PROGRESS IN RELATED DRUG RESEARCH

Cholesterol originates from endogenous synthesis or diet and is eliminated primarily through biliary secretion. A significant increase in cholesterol synthesis was found in patients with NAFLD and was positively correlated with liver fat content,[242] while increased cholesterol intake led to more severe steatosis.[243] Although statins have been shown to be effective in reducing the risk of NAFLD and have cardiovascular protective abilities,[244,245] and treating mice with atorvastatin mitigated liver and blood vessel damage caused by HFD while increasing bile acid synthesis and excretion.[246] Moreover, in view of its potential liver damage and the exact effects of cholesterol metabolic homeostasis on atherosclerotic disease, drug research targeting NR therapy for NAFLD is still particularly important. GFT505, a dual PPAR-α/δ agonist, is a promising novel agent for the treatment of NAFLD and has been shown to improve insulin sensitivity, lipids, and liver enzymes in patients with MetS or prediabetic abdominal obesity in phase II clinical trials.[247,248] Low doses of thyroid hormone effectively and safely reduced hepatic fat content in men with type 2 diabetes mellitus and NAFLD,[249] and oral selective THR-β agonist MGL-3196 significantly reduced hepatic fat accumulation in a multicenter study.[250] LXR, a key NR regulating cholesterol effection and transport, and its reverse

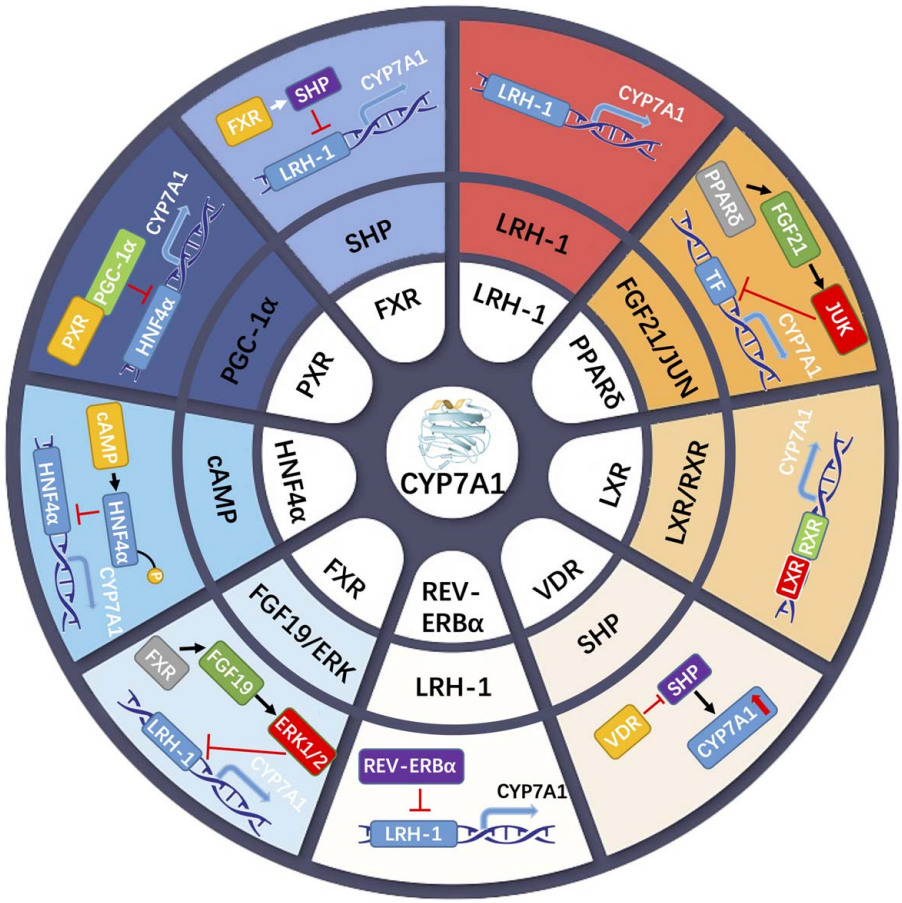

FIGURE 2 The molecular mechanism of nuclear receptor regulation on the rate-limiting enzyme CYP7a1 in bile acid synthesis. The inner ring represents the key nuclear receptor. The intermediate ring represents the factor or pathway that the nuclear receptor acts on. The outer ring is a model graph. Abbreviations: CYP7A1, cytochrome P450; FXR, farnesoid X receptor; HNF4α, hepatocyte nuclear factor 4 alpha; LXR, liver X receptor; PPAR, peroxisome proliferator-activated receptor; retinoid X receptor; SHP, small heterodimer partner.

stimulant SR9238 inhibited liver steatosis induced by high-fat diet in mice[251] and alleviated inflammation and fibrosis in mouse models of NASH.[252] Obeticholic acid (OCA), also known as INT747, is a selective FXR agonist that has been entered into clinical studies. OCA can significantly improve insulin sensitivity and reduce markers of liver inflammation and fibrosis, thereby improving NAFLD progression.[253] OCA reduced blood cholesterol levels in a Western diet and STZ-induced insulin deficiency and hyperglycemia mouse model.[254] In addition, in a multicenter study, OCA therapy improved NAFLD-induced steatosis and hepatocellular ballooning and was well tolerated, with pruritus being the most common adverse event.[212]

CONCLUSIONS

The dysregulation of NRs disrupts the comprehensive control of energy metabolism via the gut-liver-adipose axis, leading to the onset of NAFLD, with the imbalance of cholesterol homeostasis playing a crucial role. The effects of NRs on cholesterol metabolism are complex, as they are linked to both fatty acid and glucose metabolism and may appear simultaneously. Although the activation of LXR and PXR increases steatosis, PPAR and FXR reduce steatosis; interestingly, hepatic inflammation is downregulated by the activation of these receptors. This may represent a protective mechanism as it simulates the weakened activation of TLR4 by lipopolysaccharides, making the liver highly resistant to lipotoxicity. During the progression of NAFLD, FXR appears to have an antifibrotic effect; however, its role in human NASH requires further investigation. Nur77 is highly expressed in HCC and cirrhosis; however, this does not negate its protective role in the initial stages of NAFLD. Novel treatment strategies are required that provide the beneficial effects of NR activation while minimizing adverse metabolic effects. Such strategies, which are currently under development, include dual receptor agonists, tissue-specific agonists/antagonists, and the use of FGF21. Chinese herbal medicine has also shown substantial therapeutic potential in targeting some NR targets in RCT.[255,256] Furthermore, the impact of NR cross talk in NAFLD may be profound; for example, the synergistic or regulatory effects of

HNF4α, LXR, and Nur77 on the regulation of cholesterol efflux and the cascade effect of PPARγ and LXR in RCT regulation. However, more research is warranted to explore the mechanisms of cross talk between NRs.

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CONFLICTS OF INTEREST

The authors have no conflicts to report.

ORCID

Zhichi Li https://orcid.org/0009–0003–8043–7607
Difei Wang https://orcid.org/0000–0002–1118–658X

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