Role of liver X receptors in the pathogenesis and treatment of chronic liver disease (Review)

HONGHUI YOU[1*], XIANGJUN TANG[1*], XIAOYAN FU[1*], JIAQI ZHOU[1], LIYUAN WANG[1], HONGXIA ZHANG[2], XIANHONG DU[1], SHUJUAN LIANG[1] and MEIFANG LIU[1]

[1]Key Laboratory of Immune Microenvironment and Inflammatory Disease Research in Universities of Shandong Province, School of Basic Medical Sciences, Shandong Second Medical University, Weifang, Shandong 261053, P.R. China; [2]Department of Nephrology, Affiliated Hospital of Shandong Second Medical University, Weifang, Shandong 261041, P.R. China

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Abstract. Liver X receptors (LXRs), transcription factors belonging to the nuclear receptor superfamily, exist as two isoforms, LXRα (NR1H3) and LXRβ (NR1H2), that orchestrate cholesterol absorption, transport and excretion. Beyond their canonical roles in lipid homeostasis, LXRs modulate glucose metabolism, inflammatory responses and cellular proliferation. Emerging evidence implicates dysregulated LXRs activity in the pathogenesis of chronic liver diseases (CLDs), including viral hepatitis, metabolic dysfunction-associated steatotic liver disease and hepatocellular carcinoma. However, the therapeutic potential of LXRs modulation remains paradoxical: While activation mitigates hepatic injury by maintaining cholesterol homeostasis and suppressing inflammation, concurrent upregulation of sterol regulatory element-binding protein 1c exacerbates lipogenesis, potentially aggravating hepatosteatosis. The present review synthesized current insights into the dual regulatory mechanisms of LXRs in CLDs, critically evaluates their context-dependent roles and highlights the imperative to balance therapeutic efficacy with metabolic side effects in future drug development.

Correspondence to: Professor Shujuan Liang or Dr Meifang Liu, Key Laboratory of Immune Microenvironment and Inflammatory Disease Research in Universities of Shandong Province, School of Basic Medical Sciences, Shandong Second Medical University, 7166 Baotong West Street, Weifang, Shandong 261053, P.R. China
E-mail: liangshj@sdsmu.edu.cn
E-mail: lmf00719@163.com

*Contributed equally

Abbreviations: CYP7A1, cholesterol 7α-hydroxylase; CLDs, chronic liver diseases; FAS, fatty acid synthase; HDL, high-density lipoprotein; HBx, hepatitis B virus X protein; HCC, hepatocellular carcinoma; iNOS, inducible nitric oxide synthase; LDLR, low-density lipoprotein receptor; LXRs, liver X receptors; MASLD, metabolic dysfunction-associated steatotic liver disease; RCT, reverse cholesterol transport; SREBP-2, sterol regulatory element binding protein 2; SREBP-1c, sterol regulatory element-binding protein 1c; SGLT2, sodium-glucose cotransporter 2; ABCA1, ATP-binding cassette transporter A1; TG, triglyceride

Key words: liver X receptors, cholesterol metabolism, lipid metabolism, chronic liver disease, hepatocellular carcinoma

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1. Introduction

Chronic liver disease (CLD), characterized by persistent hepatic inflammation and progressive fibrosis, poses a formidable global health burden as a leading cause of mortality (1). Major etiological drivers include alcohol abuse, obesity-associated metabolic dysregulation and chronic viral hepatitis (HBV/HCV). Notably, Non-alcoholic fatty liver disease, now reclassified as metabolic dysfunction-associated steatotic liver disease (MASLD) to reflect its metabolic etiology, is a major chronic liver condition that accounts for >50% of CLD cases (2). MASLD pathogenesis intertwines with insulin resistance, leading to hepatocellular lipid deposition, oxidative stress and cytokine-driven inflammation (e.g., TNF-α, TGF-β) that culminate in steatohepatitis and cirrhosis (3). Concurrently, chronic HBV/HCV infections promote hepatocarcinogenesis through viral persistence, immune evasion and metabolic reprogramming of infected hepatocytes (4-6).

A unifying feature across CLD subtypes is metabolic dysregulation, particularly in cholesterol, lipid and glucose homeostasis, which both initiates and perpetuates disease progression. For instance, HBV/HCV exploit host cholesterol pathways for viral entry and inhibition of cholesterol synthesis can reduce the infection of a variety of human viruses, including HBV and HCV (7). MASLD-driven hepatocellular carcinoma (HCC) thrives on oncogenic lipogenesis. In the case of reduced nutritional availability, glucose metabolism

and lipid metabolism change due to the increased metabolic needs of cancer cells and play an important role in the survival of cancer cells (8-10). In summary, disorders of cholesterol metabolism, lipid metabolism and glucose metabolism are not only the causes of CLD, but also play an important role in its pathological development. The interaction among these metabolic pathways may lead to liver cell damage, inflammation and fibrosis, affecting the prognosis and quality of life of patients. Therefore, it is important to explore the interventions for these metabolic abnormalities in the treatment of CLD.

Liver X receptors (LXRs) are one of the key regulators of metabolic diseases and are also involved in the development of CLD. The role of LXRs in CLD has a dual nature and can play a protective role or show pathogenicity, which is more severe in specific cases. Activation of LXRs helps regulate cholesterol metabolism, reduces liver inflammation and protects liver cells from damage. It has been reported that LXRs reduce cholesterol levels by upregulating target genes related to reverse cholesterol transport, cholesterol conversion to bile acids and intestinal cholesterol absorption [such as ATP-binding cassette transporter (ABCA1), ATP-binding cassette transporter G1 (ABCG1), ATP-binding cassette transporter G5 (ABCG5), and ATP-binding cassette transporter G8 (ABCG8), phospholipid transporters, ApoE and cholesterol 7α-hydroxylase (CYP7A1)] (11). LXRs activation can effectively reduce the inflammatory response by inhibiting the expression of inflammatory mediators and inflammatory genes (12). However, when the disease is accompanied by metabolic abnormalities, excessive activation of LXRs can lead to lipid accumulation and further liver damage, thereby aggravating the condition. LXRs also directly regulates the expression of a number of genes involved in fatty acid synthesis, including genes encoding sterol regulatory element-binding protein 1c (SREBP-1c), a major transcriptional regulator of fatty acid synthesis. In addition, the net effect of LXRs activation is increased levels of long-chain polyunsaturated fatty acids, increased triglyceride synthesis and increased hepatic triglyceride secretion in the form of very low-density lipoprotein granules (13,14). In fact, LXRs ligands T0901317 and GW3965 were originally designed to treat atherosclerosis, but they can induce severe hypertriglyceridemia and fatty liver (15-17). These two symptoms are common in MASLD (18). Due to the side effects of LXRs, the development of LXRs agonists has been limited. Currently, there are no FDA-approved drugs related to LXRs available for use, so it is particularly important to study the regulatory mechanism of LXRs in CLD. These observations underscore the therapeutic potential of targeting metabolic regulators such as LXRs, which sit at the nexus of lipid metabolism, inflammation and cellular proliferation. The present review summarized the latest research progress on the role of LXRs in different stages of CLD and its positive and negative regulatory mechanisms.

2. Definition and functions of LXRs

Structural definition and tissue distribution. Identified from hepatic cDNA libraries, LXRs derive their name from predominant expression in the liver (19). As ligand-activated transcription factors, LXRs heterodimerize with retinoid X receptors to bind LXRs response elements in target genes. LXRs is a transcription factor of the nuclear receptor superfamily, mainly including two subtypes: LXRα (encoded by Nr1h3) and LXRβ (encoded by Nr1h2) (20). LXRα exhibits tissue-specific enrichment in the liver, intestine and adipose tissue, whereas LXRβ displays ubiquitous expression (21). Endogenous ligands include oxysterols [such as 22(R)-hydroxycholesterol], cholesterol derivatives that activate LXRs upon intracellular accumulation. For example, oxysterols can directly bind to LXRα and LXRβ receptors, activate these receptors and promote their binding to specific DNA sequences, thereby regulating the expression of downstream genes.

Cholesterol homeostasis: A central regulatory axis. Cholesterol is an essential molecule required for maintaining cell structure and is crucial for various normal biological functions (22). Cholesterol metabolism is tightly regulated in normal cells. Of total cholesterol in the human body ~80% is typically synthesized endogenously, while 20% is obtained through diet. It exists in free form or as a cholesteryl ester and fatty acids (23). Excess cholesterol accumulation in the liver or blood (hypercholesterolemia) can lead to pathological consequences such as liver steatosis and atherosclerosis (24). In addition to atherosclerosis, to which is most directly related, the accumulation of cholesterol in cells can directly lead to abnormal mitochondrial function in liver cells, which in turn triggers apoptosis or induces inflammatory reactions in adjacent cells, eventually leading to hepatitis and liver fibrosis (25). LXRs govern cholesterol metabolism through three synergistic mechanisms (Fig. 1): The first is inhibition of *de novo* synthesis: LXRs activation inhibits SREBP-2, thus reducing 3-Hydroxy-3-methylglutaryl-coenzyme A reductase expression, curtailing cholesterol biosynthesis (26). The second is promotion of reverse cholesterol transport (RCT): LXRs activation also reduces cholesterol uptake and promotes its transport to high-density lipoprotein (HDL) by regulating low-density lipoprotein receptor (LDLR) and inducing ABCA1/ABCG1 transporter expression. HDL transports cholesterol to the liver, which is further converted into bile acids and excreted through bile (21,27-30). The third is bile acid conversion: LXRs activation promotes the conversion of cholesterol to bile acids by increasing the expression of CYP7A1 and enhances cholesterol hydroxylation, driving bile acid synthesis and fecal excretion (31-33). CYP7A1 is a classical target gene of LXRs in rodents. However, in humans, the response of CYP7A1 to LXRs activation is very weak or even absent. In short, these pathways collectively prevent cytotoxic cholesterol overload, which triggers mitochondrial dysfunction, apoptosis and NLRP3 inflammasome activation in hepatocytes and dysregulated LXRs signaling, thus links hypercholesterolemia to MASLD progression and atherogenesis (34).

Lipid metabolism, glucose metabolism and inflammatory networks. Lipids are an important form of energy storage in the body and it is also an important part of cell membranes and signaling molecules. SREBP-1c is a core transcriptional activator of fatty acid biosynthesis, which is mainly responsible for maintaining lipid homeostasis and regulating fatty acid synthesis. Its importance in lipid metabolism is

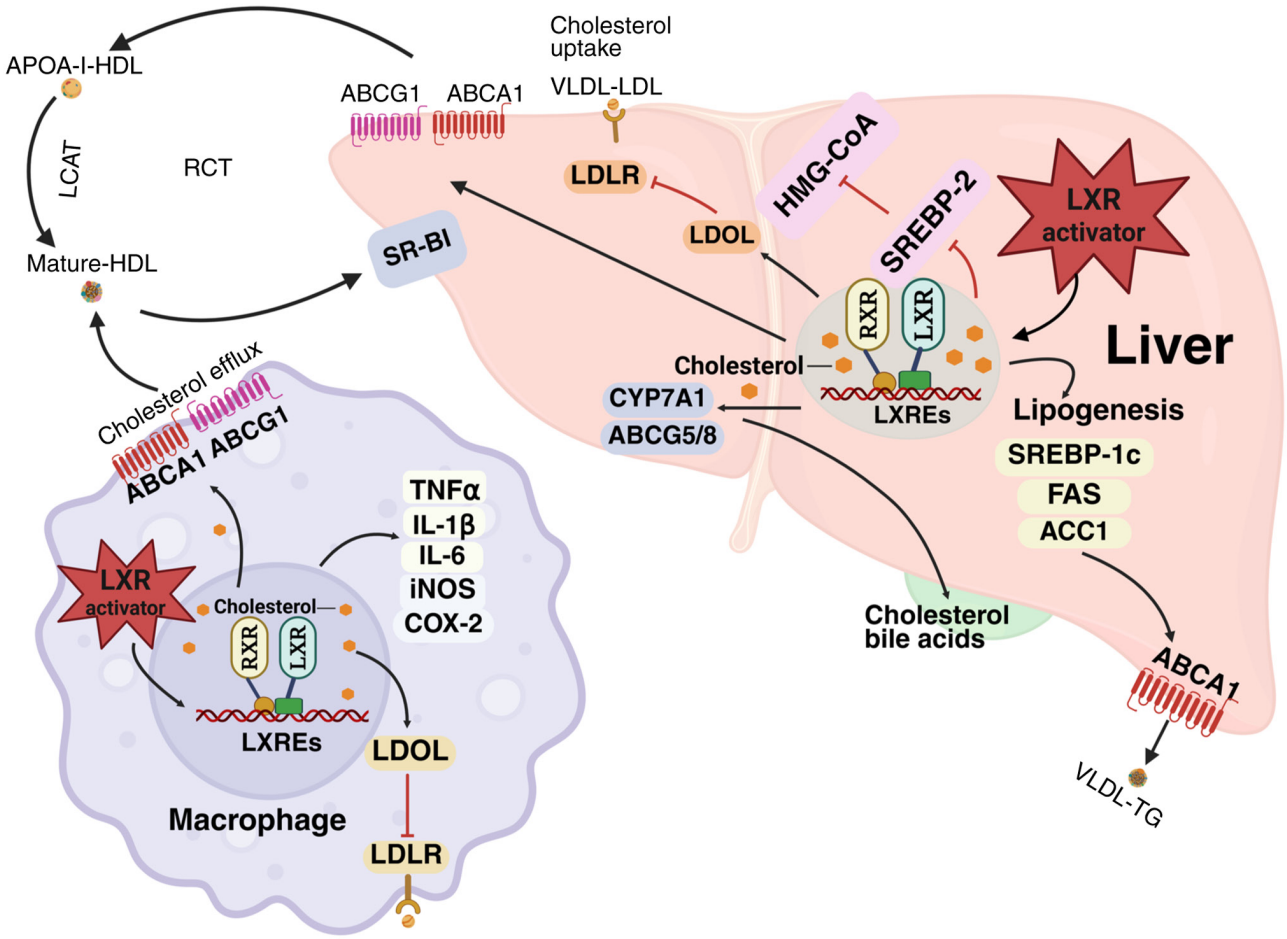

Figure 1. Mechanisms of LXRs in regulating cholesterol and lipid metabolism and inflammation. In terms of cholesterol metabolism, LXRs promote RCT by transcriptionally activating transporters such as ABCA1/ABCG1, negatively regulating LDLR and SREBP-2-mediated cholesterol uptake and synthesis pathways and activating rate-limiting enzymes such as CYP7A1 to promote cholesterol hydroxylation and bile acid conversion. In lipid metabolism, LXRs markedly enhance fatty acid *de novo* synthesis by inducing key factors such as SREBP-1c and FAS. Additionally, LXRs promote cholesterol efflux by regulating macrophage function and maintain cholesterol homeostasis, thereby reducing inflammatory responses and providing protection against inflammatory diseases. LXRs, liver X receptors; RCT, reverse cholesterol transport; CYP7A1, cholesterol 7α-hydroxylase; FAS, fatty acid synthase; LDOL, inducible degrader of LDLR; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; SREBP-1c, sterol regulatory element-binding protein 1c; ACC1, acetyl-CoA carboxylase 1; ABCA1, ATP-binding cassette transporter A1; HDL, high-density lipoprotein; VLDL, very-low-density lipoprotein; LDLR, LDL receptor; TG, triglyceride; TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; iNOS, inducible nitric oxide synthase; COX-2, cyclooxygenase-2; LCAT, lecithin-cholesterol acyltransferase; APOA-I, apolipoprotein A-I; SR-BI, scavenger receptor class B type I.

self-evident (35). Studies in LXRs-deficient mice have shown that the expression level of SREBP-1c mRNA in the liver is markedly decreased and the mRNA levels of lipogenic enzymes affected by it are also decreased (36). This indicates that LXRs are key transcriptional regulators involved in lipid metabolism in the liver and their adipogenic activity is mainly achieved by inducing the transcription of the gene encoding SREBP-1c. Direct transcriptional activation of SREBP-1c induces lipogenic enzymes, such as acetyl-CoA carboxylase 1 and fatty acid synthase (FAS) (36-38). The liver is an important organ of insulin sensitivity and is essential for maintaining blood glucose homeostasis. Insulin resistance can lead to changes in metabolic gene expression and glucose metabolism disorders. LXRs not only participates in cholesterol and lipid metabolism, but also plays an important role in glucose metabolism (39). LXRs activation inhibits the function of sodium-glucose cotransporter 2 (SGLT2) by reducing the expression of SGLT2 protein. Suppression of SGLT2 attenuates renal glucose reabsorption, implicating LXRs in systemic glucose regulation (40). In addition, inflammation is considered to be a major driver of the development of a number of chronic diseases. LXRs also plays an important role in the regulation of inflammation. LXRs inhibits inflammation through two main mechanisms. The first is LXRs agonists repress NF-κB via increasing the level of MyD88 mRNA alternative splicing short form, thereby reducing the production of inflammatory cytokines (such as TNF-α, IL-1β and IL-6) (41). The second is to enhance macrophages cholesterol efflux, dampening pro-inflammatory cytokine production (42). In general, this functional pleiotropy positions LXRs as master regulators of metabolic-inflammatory crosstalk, yet also underlies their context-dependent duality in CLD pathogenesis.

3. The role of LXRs in CLD

Viral hepatitis

Antiviral effect. The expression of HBV is not only related to liver metabolism, but HBV also actively interferes with liver

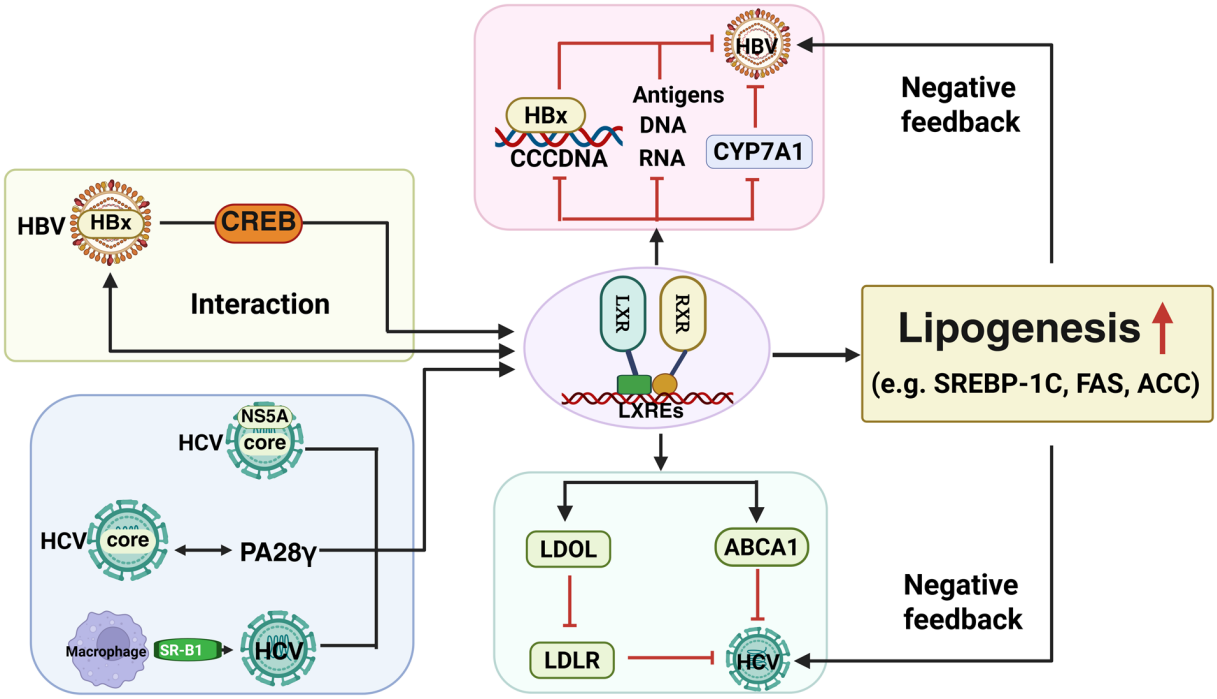

Figure 2. The relationship between LXRs and hepatitis. The role of LXRs in hepatitis exhibits a dual nature: On one hand, its activation can effectively inhibit the replication of HBV and HCV viruses; on the other hand, it may also exacerbate HBV- and HCV-related hepatic steatosis by promoting lipid accumulation. LXRs, liver X receptors; HBV, hepatitis B; SREBP-1c, sterol regulatory element-binding protein 1c; FAS, fatty acid synthase; ACC, acetyl-CoA carboxylase; CYP7A1, cholesterol 7α-hydroxylase; HBx, HBV X protein; cccDNA, covalently closed circular DNA; CREB, cAMP response element-binding protein; PA28γ, proteasome activator 28γ; LDLR, low-density lipoprotein receptor; LDOL, inducible degrader of LDLR; ABCA1, ATP-binding cassette transporter A1.

metabolic pathways. This unique interaction between HBV and liver metabolism is called the 'metabolovirus' model of HBV expression (43). Thus, regulation of the metabolism of the host cell represents a viable approach to antiviral intervention. Ezetimibe is an FDA-approved drug that inhibits liver cholesterol renewal. It has been shown to inhibit HCV and HBV infection by regulating liver cholesterol uptake (44). LXRs is the main transcriptional regulator of a series of genes involved in cholesterol uptake, transport, efflux and excretion (45). The pleiotropic effects of LXRs agonist therapy may also contribute to antiviral activity. For example, 22(S) -hydroxycholesterol, a LXRs ligand, is reported to block HBV infection in dHepaRG cells (46). The activation of the LXRs pathway in HBV-infected primary human hepatocytes can effectively inhibit HBV, mainly through three mechanisms (Fig. 2): Reducing the production of viral RNA, DNA and antigens; blocking the interaction between Hepatitis B virus X protein (HBx) and viral replication template covalently closed circular DNA (cccDNA) and reducing the transcription level of cccDNA; and the destruction of the expression of downstream LXRs' target gene CYP7A1 (47). In addition to effectively inhibiting HBV replication, the role of LXRs in HCV infection is also notable. LXRs can block and weaken HCV infection through a variety of mechanisms, thereby enhancing the host's antiviral ability. Although the exact mechanism that regulates the entry of HCV into hepatocytes is unclear, LDLR has been shown to be necessary for the entry of infectious HCV particles. LXRs controls the ubiquitination and degradation of LDLR by regulating the expression of inducible degrader of LDLR (LDOL), thereby blocking HCV infection (48). It has been shown that the entry of HCV cells requires cholesterol homeostasis and intact cholesterol-rich membrane microdomains; however, a major regulator of cellular cholesterol and phospholipid homeostasis is the ABCA1 transporter (49). LXRs agonist GW3965 can inhibit HCV cell entry by activating LXRs and upregulating the expression of ABCA1 (50).

Contradictory effects of LXRs. In addition to inhibiting HCV replication, the function of LXRs is also impaired by HCV. HCV NS5A and core proteins promote intracellular lipid accumulation by enhancing the expression and transcriptional activity of LXRα. This accumulation of lipids is achieved by activating the LXRs response element, leading to upregulation of genes associated with adipogenesis (such as SREBP-1c, PPAR-γ and fatty acid synthase) (51). In the liver of HCV patients, LXRα and its related adipogenic genes (such as PPARγ and SREBP-1c) and inflammatory genes are abnormally increased, suggesting that LXRs plays an important role in liver lipid accumulation (52). Specifically, HCV core protein enhances the activity of LXRα/RXRα-dependent SREBP-1c promoter by interacting with PA28γ, thereby promoting liver steatosis (53). Therefore, although LXRs activation can inhibit HCV replication, it may also aggravate HCV-related liver steatosis by promoting lipid accumulation. This dual role reveals the complex role of LXRs in HCV infection: on the one hand, it can be used as a potential target for antiviral therapy; on the other hand, it may lead to abnormal lipid metabolism in pathophysiology. In addition, HCV infection also leads to metabolic and immune changes in liver macrophages, which further aggravates lipid accumulation and inflammatory response and may develop into steatohepatitis and fibrosis.

Studies have shown that HCV RNA can accumulate and persist in macrophages, although it does not express viral proteins. After macrophages were exposed to HCV, the levels of cholesterol efflux-related protein ABCA1 and SREBP-1c increased. Macrophages recognize HCV through scavenger receptor B1 (SR-B1), activate LXRα, lead to increased lipid and cholesterol and trigger metabolic changes in HCV-related CLDs (54). This series of mechanisms indicates the key role of LXRs in HCV infection and related liver diseases. Similarly, HBV-related pathological mechanisms also involve the role of LXRs. HBx is not only a key regulator of viral replication and infection, but also interacts with a variety of signaling pathways in host cells, which has a fresh impact on the pathogenesis of liver (55). It has been found that increased expression of HBx leads to lipid accumulation in hepatocytes, which is mediated by SREBP1 and PPARγ (56). It was further elucidated the molecular mechanism of HBx-induced lipid accumulation in hepatocytes. It has been shown that HBx interacts with LXRα, enhances the binding of LXRα to LXRs response element (LXRE) and then upregulates SREBP1 and FAS, resulting in an increase in lipid in hepatocytes (57). In addition, in HBV-related HCC, HBx also induces the transactivation of LXRα by recruiting CREB-binding protein to the promoter of the target gene, thereby activating the target gene of lipid production and further aggravating lipid accumulation in hepatocytes (58). In summary, the role of LXRs in HBV and HCV infection is very complex. Although the activation of LXRs can inhibit viral replication, it can also lead to changes in lipid metabolism, thus providing a more favorable living environment for the virus. It is hoped that future research will help to further understand the dual role of LXRs in viral infection in order to develop new therapeutic strategies.

MASLD

Reduced inflammation and fibrosis. The pathogenesis of MASLD is closely linked to insulin resistance, which leads to abnormal accumulation of free fatty acids in hepatocytes (59). This accumulation heightens the cells' sensitivity to oxidative stress, mitochondrial dysfunction and endoplasmic reticulum stress, prompting the secretion of inflammatory cytokines such as TNF-α, TGF-β and monocyte chemoattractant protein-1 (MCP-1) (60). As previously reported, LXRs activation can limit intracellular cholesterol levels by inducing reverse cholesterol transport, increasing bile acid production and inhibiting intestinal cholesterol absorption. In addition to its key role in cholesterol homeostasis, LXRs is also an important regulator of inflammatory gene expression. Ligand-activated LXRs attenuates the induction of classical inflammatory genes [such as inducible nitric oxide synthase (iNOS), cyclooxygenase-2, matrix metalloproteinase-9 (MMP-9) and various chemokines] stimulated by LPS, TNF-α and IL-1β (12). LXRs plays a key regulatory role in MASLD (Fig. 3). Activation of LXRs can alleviate the liver injury of MASLD by inhibiting JNK and PI3K signaling pathways and reducing the expression of pro-inflammatory markers such as TNF-α and iNOS (61). In addition, the destruction of Ser196 phosphorylation (S196A) in LXRα prevents cholesterol accumulation and reduces liver inflammation and fibrosis. This mechanism helps to delay the progression of MASLD. However, after disrupting S196A in LXRα, acetylation of the key histone H3K27 can upregulate Ces1f and SREBP-1c and induce hepatic steatosis (62). These results indicate that LXRs plays an important role in regulating inflammatory response and can inhibit liver inflammation and liver fibrosis. However, activation of LXRs also promotes adipogenesis.

Reduced hepatic steatosis. Although LXRs may have a protective effect in some ways, in the context of MASLD, the activation of LXRs often leads to the disorder of lipid metabolism and promotes the aggravation of the disease. The expression of LXRα, SREBP-1c, ACC and FAS in the liver of MASLD patients is markedly upregulated. It is suggested that LXRs and its downstream target genes are involved in lipid metabolism of MASLD (63). LXRs promotes adipogenesis by regulating key factors such as SREBP-1c and carbohydrate response element-binding protein, which may lead to hypertriglyceridemia and hepatic steatosis (64,65). In addition to activating LXRs, the removal of inhibitory histone markers histone H3 di-methylation at lysine 9 (H3K9me2) and H3K9me3 on LXRE can also upregulate the expression of LXRα-dependent adipogenic genes, leading to triglyceride (TG) accumulation and MASLD (66). Therefore, inhibition of LXRs activity is considered to be a potential therapeutic strategy in some cases (Table I). As an antagonist of LXRs, meso-dihydroguaiaretic acid (MDGA) inhibits activation of the LXRα ligand-binding domain by competitively binding to the pocket for agonist T0901317, reduces the transcriptional expression of lipogenesis-related LXRα coactivator protein and downstream target genes involved in fatty acid synthesis, and thereby reduced lipid accumulation in mice administered with T0901317 or fed with a high-fat diet. These results suggest that MDGA has the potential to attenuate nonalcoholic steatosis mediated by selective inhibition of LXRα in the liver of mice (67). N-(4-trifluoromethylphenyl) 3,4-dimethoxycinnamamide is a compound that inhibits the ligand binding domain of LXRα. It plays a role by forming hydrogen bonds with Arg305 in the H5 region, affecting the dissociation of thyroid hormone receptor-associated protein/vitamin D receptor-interacting protein coactivator and the recruitment of nuclear receptor corepressor to regulate the transcriptional control exerted by LXRα, thereby attenuating LXRα-induced adipogenesis and fatty liver (68).

A number of natural compounds have multiple biological activities and can act on multiple metabolic pathways at the same time to improve a number of aspects related to MASLD (Table I), such as lipid metabolism, inflammatory response and oxidative stress, which makes them more effective in comprehensive treatment. Acanthoic acid (AA) is a diterpene isolated from *Acanthopanax koreanum* Nakai (Araliaceae), which has anti-inflammatory and hepatoprotective effects. In a MASLD mouse model, AA markedly reduced hepatic steatosis and fibrosis in MASLD mice and steatotic AML 12 cells by activating FXR/LXRs to reduce the expression of SREBP-1 and target genes, upregulate the expression of PPARα and downregulate the expression of PPARγ (69). Natural compounds may enhance the body's own metabolic capacity by regulating endogenous metabolic pathways and signaling pathways, thus playing a synergistic role in improving MASLD. Research shows that 4,5-dihydroxyanthraquinone-2-carboxylic acid (Rhein) may reduce hepatic TG accumulation via two pathways. First, Rhein decreases *de novo* lipogenesis by

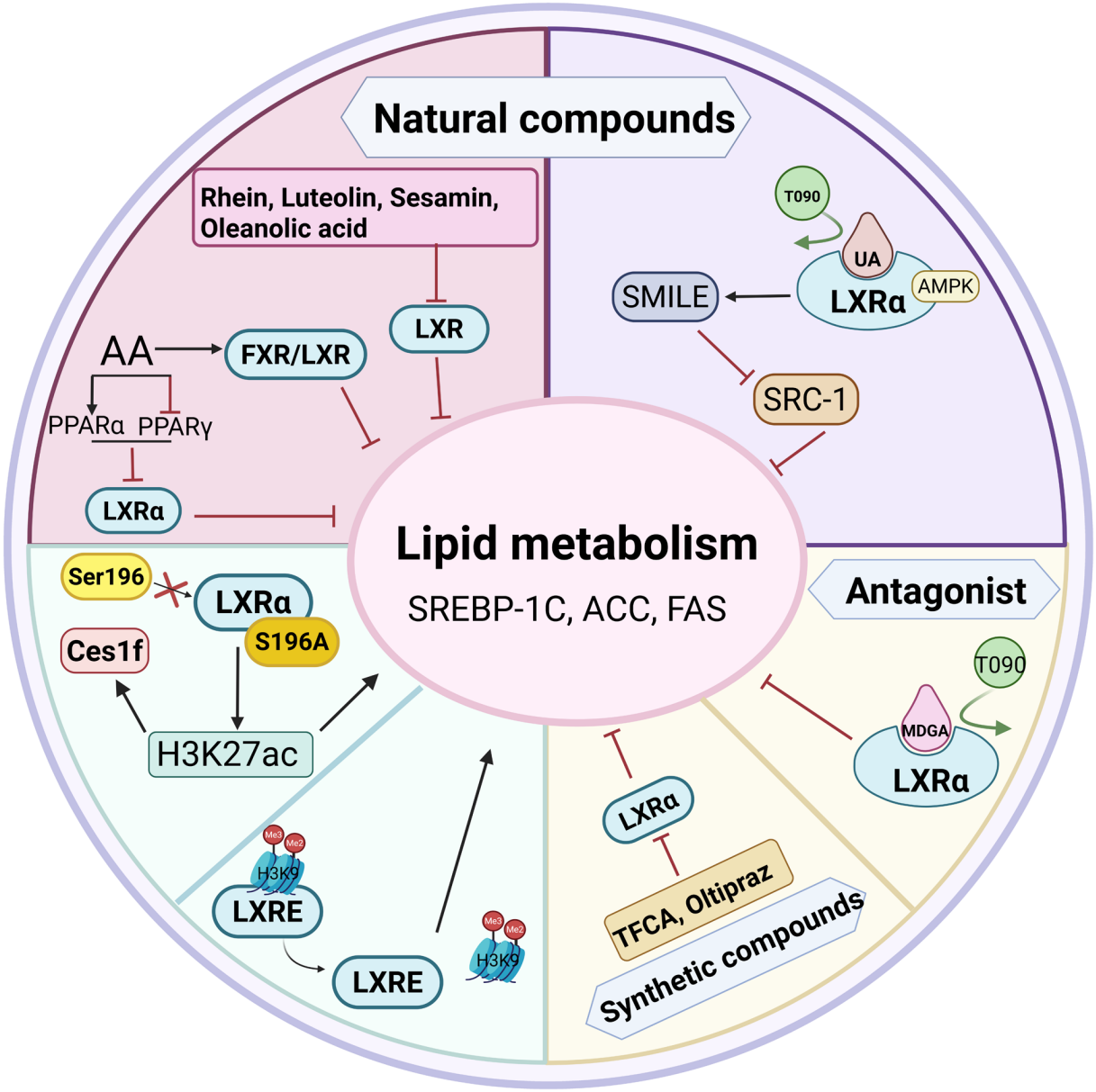

Figure 3. The relationship between LXRs and MASLD. Natural compounds (Rhein, sesamin, luteolin, oleanolic acid, AA) and compounds (TFCA) reduce lipid synthesis by inhibiting LXRs. The LXRs antagonist MDGA and the natural compound UA inhibit the activation of the LXRα ligand binding domain by competitively binding to the pocket of the agonist T0901317 and reduce lipid accumulation in mice. However, the removal of the inhibitory histone markers H3K9me2 and H3K9me3 on LXRE upregulates the expression of LXRα-dependent adipogenic genes. In addition, the key histone H3K27ac can upregulate Ces1f and SREBP-1c and induce hepatic steatosis due to the destruction of Ser196 phosphorylation (S196A) in LXRα. LXRs, liver X receptors; MASLD, metabolic dysfunction-associated steatotic liver disease; Rhein, 4,5-dihydroxyanthraquinone-2-carboxylic acid; AA, acanthoic acid; TFCA, N-(4-trifluoromethylphenyl)-3,4-dimethoxycinnamamide; H3K9me2, histone H3 di-methylation at lysine 9; H3K27ac, histone H3 lysine 27 acetylation; SREBP-1c, sterol regulatory element-binding protein 1c; SMILE, small heterodimer partner-interacting leucine zipper protein; SRC-1, steroid receptor coactivator-1; UA, Ursolic acid; AMPK, AMP-activated protein kinase; MDGA, meso-dihydroguaiaretic acid; H3K9, histone H3 lysine 9; Ces1f, carboxylesterase 1F; Ser196, serine 196; S196A, serine 196 to alanine; PPAR, peroxisome proliferator-activated receptor; FXR, farnesoid X receptor.

directly suppressing LXRs-mediated SREBP-1c expression. Second, Rhein improves MASLD and related diseases through LXRs-mediated energy balance, metabolic regulation pathways and immunomodulatory activities involved in hepatic steatosis (70). Ursolic acid (UA) is a plant triterpene compound that binds competitively with T090 at the LXRα ligand binding domain that increases the co-repressor protein SMILE and reduces the co-activator SRC 1 through AMPK, so as to reduce the expression of SREBP-1c, FAS and ACC genes, thereby reducing liver lipid accumulation and improving blood lipid levels. The RCT stimulation of LXRα is retained and enhanced, providing a potential treatment for MASLD (71). Natural compounds such as luteolin, sesamin and oleanolic acid have shown significant potential in improving liver steatosis. Luteolin can not only inhibit the activation of LXRs, but also further reduce lipid synthesis by downregulating the expression of SREBP-1c, while maintaining glycogen storage and helping to improve liver metabolism (72). Sesamin (73) and oleanolic acid (74) attenuate ligand-induced adipogenesis through a similar mechanism, thereby reducing fat accumulation in the liver. The study of these natural compounds provides an important theoretical basis for the development

Table I. Compounds and natural products activate/inhibit LXRs.

First author/s, year	Name	Source	Activation/ inhibition	Medical effects	(Refs.)
Sim, 2014	Meso-Dihydroguaiaretic acid	A dibenzylbutane lignan isolated from *Machilus thunbergii*	Suppresses LXRα transcription	• Expression of adipogenic mRNA in HepG2 cells: Srebf-1c ↓; Fas ↓; SCD1 ↓; ACC ↓; ACLY ↓; Elovl6 ↓ • Expression of VLDL assembly mRNA in HepG2 cells: Mtp ↓; ApoB ↓ • Expression of biliary cholesterol secretion mRNA in HepG2 cells: Abcg5 ↑; Abcg8 ↓ Expression of adipogenic mRNA in HepG2 cells: Hmgcs1 ↓; SQS1 ↓	(67)
Sim, 2015	N-(4-trifluoromethylphenyl) 3,4-dimethoxycin-namamide	N-(4-trifluoromethylphenyl) 3,4 dimethoxycinnamamide is a new chemical entity with a cinnamamide structure	Suppresses LXRα transcription	• Expression of adipogenic mRNA in AML12 cells: Srebf-1c ↓; Fas ↓; Scd- 1 ↓; Serum ALT, TG levels ↓; Serum HDL ↑ • Expression of adipogenic gene mRNA in mice: Srebf-1c ↓; Fas ↓	(68)
Han, 2019	Acanthoic acid	A pimaradiene diterpene isolated from *Acanthopanax koreanum* Nakai (Araliaceae)	Activation of LXRs transcription	• Serum ALT, AST, TG levels ↓; Tissue TG ↓ • Expression of adipogenic gene mRNA in mice: Srebf-1c ↓; Fas ↓; SCD1 ↓; ACLY ↓; Hepatic ↑; PPARα Hepatic PPARγ ↓ • Expression of pro-fibrogenic gene mRNA in mice: α-SMA ↓; collagen I ↓; TIMP-1 ↓; Hepatic SIRT1 ↑; Hepatic p-AMPKα/ AMPKα ↑; Hepatic p-LKB1/ LKB1 ↓	(69)
Sheng, 2011	Rhein (4,5-dihydroxyanthraquinone-2-carboxylic acid)	An anthraquinone and is one of the major components of *Rheum palmatum* L	Antagonist	GPDH activity ↓; LXRα, PPARγ, C/EBP-α, PGC-1, Lpl, aP2, Cd36 mRNA levels ↓; Serum TC, HDL, LDL, ALT ↓; Hepatic TG in DIO mice ↓; Hepatic SCD1, FAS mRNA and protein levels ↓; Hepatic mSREBP-1c protein level ↓	(70)
Lin, 2018	Ursolic acid	Found in several traditional Chinese medicinal herbs, such as *Cornus officinalis*	LXRα antagonist	GPDH activity ↓; LXRα, PPARγ, C/EBP-α, PGC-1, Lpl, aP2, Cd36 mRNA levels ↓; Serum TC, HDL, LDL, ALT ↓; Hepatic TG in DIO mice ↓; Hepatic SCD1, FAS mRNA and protein levels ↓; Hepatic mSREBP-1c protein level ↓;	(71)

Table I. Continued.

First author/s, year	Name	Source	Activation/ inhibition	Medical effects	(Refs.)
				Direct regulatory effects on LXRs protein structure; CoR SMILE ↑; CoA SRC-1 recruitment to the SREBP-1c promoter region ↓; LXRE-Luc and SREBP-1c-Luc activity *in vitro* ↓; HepaRG: TG and TC content ↓; mRNA expression of SREBP-1c, FAS, SCD1, ACC, ACLY, FAE ↓; Protein levels of SREBP-1c, FAS, SCD1, SRC-1 ↓	
Yin, 2017	Luteolin	A flavonoid, occurs in a broad range of vegetables, fruits and grains	Antagonist	Inhibiting the expression of LXRs target genes *in vitro*; HepG2: SREBP-1c genetranscription ↓; Serum TG levels ↓	(72)
Tai, 2019	Sesamin	Sesamin is a naturally occurring lignan in a number of dietary plants	Suppresses LXRα transcription	3xLXRE-tk Luc ↓; SREBP-1c-tk-Luc ↓; mRNA expression of FAS, SCD, ACC, ACLY, FAE ↓; mRNA expression of ABCA1 and ABCG1 ↑	(73)
Lin, 2018	Oleanolic acid	Oleanolic acid is a naturally occurring triterpenoid found in a number of plants	Suppresses LXRα transcription	• Expression of adipogenic mRNA in HepG2 cells: Srebf-1c ↓; Hepatic SREBP-1c, ACC, FAS ↓; • Expression of protein in HepG2 cells: SREBP-1c, FAS, SCD, ACLY, FAE ↓; Enhances the expression of RCT-related genes: ABCA1 ↑; ABCG1 ↑	(74)

LXRs, liver X receptors; SREBP-1c, sterol regulatory element-binding protein 1c; FASN, fatty acid synthase; SCD1, stearoyl-coenzyme A desaturase 1; ACC, acetyl-CoA carboxylase; ACLY, ATP citrate lyase; Elovl6, ELOVL fatty acid elongase 6; Mtp, microsomal triglyceride transfer protein; ApoB, apolipoprotein B; ABCG5, ATP binding cassette subfamily G member 5; ABCG8, ATP binding cassette subfamily G member 8; Hmgcs1, 3-hydroxy-3-methylglutaryl-CoA synthase 1; SQS, squalene synthase; ALT, alanine aminotransferase; TG, triglyceride; HDL, high-density lipoprotein; PPARα, peroxisome proliferator-activated receptor α; α-SMA, α-smooth muscle actin; collagen I, collagen type I; TIMP-1, tissue inhibitor of metalloproteinases 1; SIRT1, sirtuin 1; p-AMPKα, phosphorylated AMP-activated protein kinase α; p-LKB1, phosphorylated liver kinase B1; GPDH, glycerol-3-phosphate dehydrogenase; LXRα, liver X receptor α; C/EBP-α, CCAAT/enhancer-binding protein α; PGC-1, peroxisome proliferator-activated receptor gamma coactivator-1; Lpl, lipoprotein lipase; aP2, adipocyte protein 2; Cd36, cluster of differentiation 36; TC, total cholesterol; LDL, low-density lipoprotein; CoR SMILE, corepressor small heterodimer partner-interacting leucine zipper protein; CoA SRC-1, coactivator steroid receptor coactivator-1; LXRE-Luc, liver X receptor response element-luciferase; SREBP-1c-Luc, sterol regulatory element-binding protein 1c-luciferase; FAE, fatty acid elongase; ABCA1, ATP-binding cassette transporter A1.

of new therapeutic strategies, especially in the treatment of nonalcoholic fatty liver disease and other related diseases.

HCC

LXRs-related metabolic regulation and immune regulation. LXRs has been identified as a potential therapeutic target for a variety of types of cancer, including breast cancer (75), prostate cancer (76) and HCC (77-80). Its mechanism of action involves promoting cholesterol metabolism (75,76), interacting with TGF-β (78,79). The activation of LXRβ can inhibit tumor growth and innate immune response (81). Specifically (Fig. 4), LXRs activation inhibits tumor cell proliferation by promoting cholesterol catabolism (80) and reducing intracellular cholesterol levels (82). Cholesterol plays a key role in cell proliferation in physiological and tumor states and cancer cells need sufficient cholesterol to support their rapid growth. A study has found that LDLR and ACAT are overexpressed in tumor tissues of most patients with cancer, which provides support for the rapid proliferation of cancer cells (22). It has also been reported that targeting LDLR with the LXRs agonist GW3965 causes LDOL-mediated LDLR degradation and increased expression of the ABCA1 cholesterol efflux

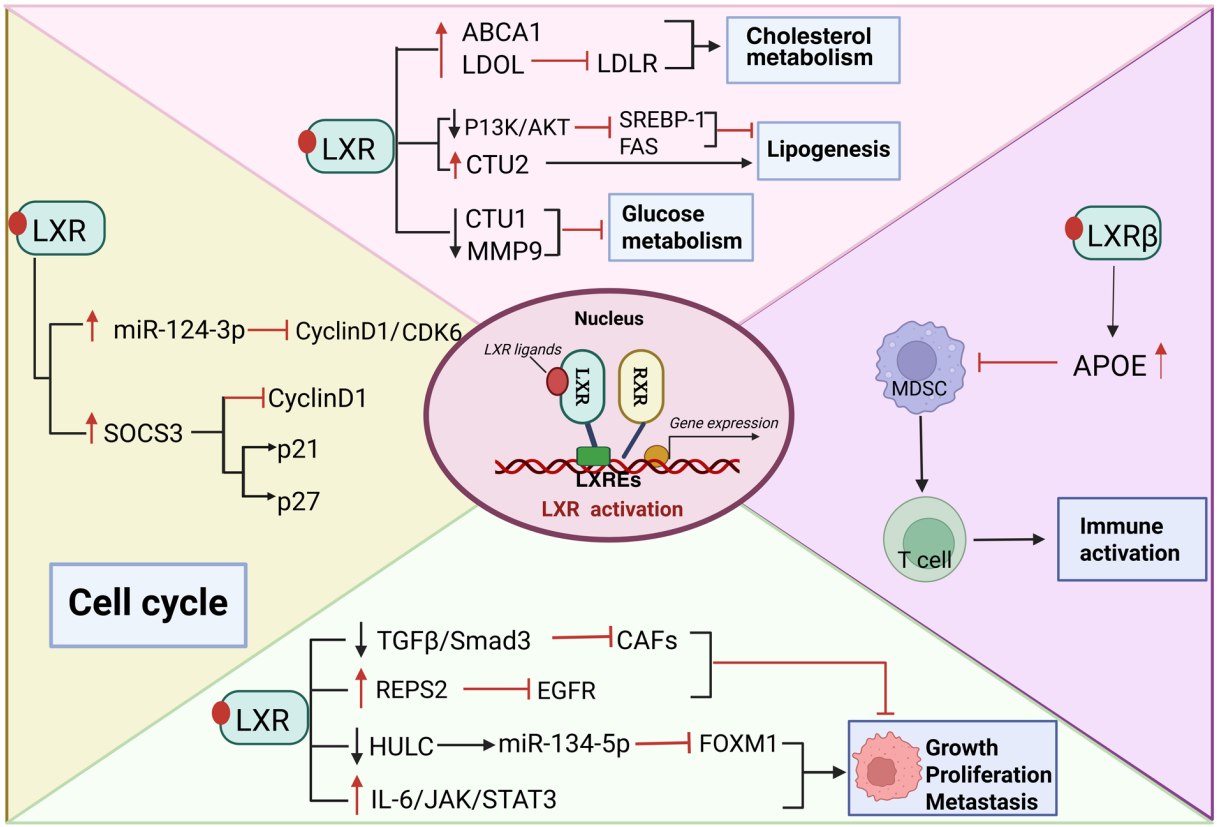

Figure 4. The role of LXRs in HCC. LXRs regulate the occurrence and development of HCC through multi-dimensional mechanisms. Firstly, LXRs directly affect the pathological process of HCC by regulating cholesterol metabolism, lipid metabolism, glucose metabolism and cell cycle. Secondly, LXRs are also involved in the regulation of HCC by regulating the growth, proliferation and migration of tumor cells. In addition, LXRs enhance the anti-tumor immune response of T cells by regulating the number of MDSC, thereby inhibiting the development of HCC at the immune level. LXRs, liver X receptors; HCC, hepatocellular carcinoma; MDSC, myeloid-derived suppressor cell; APOE, apolipoprotein E; TGFβ/Smad3, transforming growth factor-β/Smad family member 3; CAFs, cancer-associated fibroblasts; REPS2, RALBP1-associated Eps domain-containing protein 2; EGFR, epidermal growth factor receptor; HULC, highly up-regulated in liver cancer; miR-134-5p, microRNA-134-5p; FOXM1, forkhead box protein M1; IL-6, interleukin-6; JAK, Janus kinase; STAT3, signal transducer and activator of transcription 3; SOCS3, suppressor of cytokine signaling 3; miR-124-3p, microRNA-124-3p; CDK6, cyclin-dependent kinase 6; ABCA1, ATP-binding cassette transporter A1; LDLR, low-density lipoprotein receptor; LDOL, inducible degrader of LDLR; SREBP-1, sterol regulatory element-binding protein 1; FAS, fatty acid synthase; CTU, cytosolic thiouridylase subunit; MMP9, matrix metalloproteinase 9.

transporter, resulting in decreased cholesterol levels, which effectively promotes tumor cell death (83). LXRα agonists limit the expression of myofibroblast markers by antagonizing the TGFβ signaling pathway at the transcriptional level, inhibiting the differentiation of cancer-associated fibroblasts, thereby inhibiting the growth of liver cancer cells (78). In addition, it has been found that LXRs activation leads to LXRs target gene ApoE inhibiting myeloid-derived suppressor cells survival through its effect on LRP8 receptor, thereby weakening the immunosuppressive effect, enhancing the activation of T cells and triggering a strong anti-tumor response (81). Lipids are mainly processed in the liver and play an important role in the physiology of the organ and the pathological progression of a number of diseases such as metabolic syndrome and HCC (84). Enhanced adipogenesis is important for cancer cells because it provides lipids for membrane structural units, post-translational modifications of proteins and energy storage (85). In addition, LXRs are activated by oxysterols, which can cause lipotoxicity in liver cancer (86) and lipid production promotes the occurrence and development of liver cancer (87). SREBP-1c was reported to be highly expressed in liver cancer, prostate cancer and ovarian cancer (88). In addition, FAS and ACC, which are closely related to LXRs, have also been found in HCC and various other human epithelial cancers and precancerous lesions (89). Studies have found that cytosolic thioureaase 2 (CTU2) is involved in lipogenesis by directly promoting the synthesis of lipogenic proteins and have determined that CTU2 is a LXRs target gene (90). By reducing the expression of CTU2 and LXRs ligands, this approach can induce tumor cell apoptosis and inhibit cell proliferation to enhance the anti-tumor effect of HCC. Bergapten acts as a LXRα/β agonist and inhibits HCC progression by regulating PI3K/AKT and LDOL/LDLR signaling pathways. Moreover, it downregulates SREBP 1 and FAS levels through AKT inhibition to maintain lipid homeostasis, thereby exerting an anti-tumor effect (91).

LXRs regulates transcription genes. In HCC, a number of genes related to cell proliferation [forkhead box protein M1 (FOXM1), suppressor of cytokine signaling 3 (SOCS3)], invasion and migration are directly regulated by LXRs. It has been found that activated LXRα can downregulate the expression of HULC, that promotes the growth and metastasis of HCC cells and which further upregulates the expression level of miR-134-5p (inhibiting cancer cell proliferation and invasion) and inhibits the expression of FOXM1 (affecting cell proliferation and migration), thereby inhibiting the growth

of liver cancer cells (92). The high expression of miR-124-3p in LXRs-activated condition affects the formation of cyclin D1/CDK6 active complex by cyclin D1 and its binding partner CDK 6, thereby regulating the cell cycle and inhibiting the progression of HCC (93). Although LXRβ has anticancer function, LXRα-mediated SOCS3 induction is the reason for the anti-HCC effect of LXRs agonists (94). The methylation of SOCS3 gene promoter region leads to its downregulation in HCC and the re-expression of SOCS3 leads to apoptosis and cell cycle arrest (95-97). The activation of LXRs upregulates the expression of SOCS3 by enhancing the mRNA stability of SOCS3. LXRs inhibits the occurrence and development of HCC by inducing SOCS3 to downregulate cyclin D1 and downregulates p21 and p27 (98). Epidermal growth factor receptor (EGFR) is a transmembrane tyrosine kinase receptor that can be activated by a variety of ligands, thereby activating multiple signaling pathways, promoting tumor cell proliferation and metastasis and inhibiting apoptosis. It has been shown that the activation of LXRs can promote the binding of LXRs protein to LXRE in the REPS 2 promoter region, upregulate the expression of REPS 2 and inhibit EGF-mediated EGFR endocytosis and downstream activation of AKT/NF-κB, p38MAPK and ERK1/2 signaling pathways, thereby inhibiting the proliferation and migration of HCC cells and exerting anti-tumor effects (99). Malignant tumor cells increase glucose uptake by increasing the expression of glucose transporter 1 (Glut1) to meet their high energy needs (100). The upregulation of Glut1 can also promote the activity of EGFR and integrin signaling pathways, thereby enhancing the proliferation, migration and invasion of tumor cells (101). However, activation of LXRs can inhibit this process. Specifically, LXRs inhibits the progression of HCC by downregulating the expression of Glut1 and tumor invasion marker MMP9 and reducing the glucose content in HCC cells (102). Chronic activation of LXRα promotes HCC at least in part by promoting the upregulation of innate immunosuppressive factors caused by oxysterol accumulation, as well as the IL-6/Janus kinase/STAT3 signaling and complement pathways (103). If the tumor-promoting effect caused by chronic activation of LXRs is solved, its anti-tumor effect may be further improved. Tumor LXRs expression is a prognostic marker for patients with HCC. The average 5-year overall survival rate and average overall survival time of patients with low LXRs expression are markedly lower than those of patients with high LXRs levels (104). In general, LXRs play an important role in the occurrence and development of liver cancer, but research in this field is continues. Future research may reveal more details about the relationship between LXRs and liver cancer and may provide clues for the development of new strategies for the treatment of HCC.

LXRs in the progression and multifactorial interactions of CLD. LXRs, as a core transcription factor connecting metabolism and immunity, exhibit a complex role which is related to the etiology, development stage and specific cell types of the chronic diseases. For instance, LXRs is implicated throughout the pathogenic progression from viral hepatitis to hepatic fibrosis and eventually to HCC.

LXRs in viral hepatitis and progression to HCC. In viral hepatitis, LXRs primarily exerts a protective regulatory role. In the early stage of infection, it can directly interfere with the viral entry into hepatocytes. After entering the stage of chronic inflammation and fibrosis, LXRs helps mitigate excessive inflammatory responses and inhibits the activation of hepatic stellate cells by promoting macrophage cholesterol efflux (such as via its target gene ABCA1/ABCG1), thereby delaying disease progression (105). However, persistent viruses can impair this protective function of LXRs by interfering with the host transcriptional program. Crucially, in chronic hepatitis B progression, LXRα expression is specifically downregulated in Kupffer cells, leading to disordered lipid metabolism and subsequent activation of the Stat3 signaling pathway, which promotes cancer stem cell formation. Upregulation of LXRα can inhibit this process, revealing a key node of LXRs in suppressing inflammation to cancer transition (106).

LXRs in MASLD/MASH: From steatosis to cancer. By contrast, the role of LXRs in the MASLD/MASH is inherently more complex and context-dependent. In early disease stages, activation of LXRα in hepatocytes mainly through SREBP-1c-promotes *de novo* lipogenesis and directly contributes to simple steatosis. As the disease progresses to steatohepatitis and fibrosis, LXRs exerts anti-inflammatory and anti-fibrotic effects by inducing antioxidant genes and suppressing macrophage-mediated inflammation (107). However, sustained overactivation of its lipogenic pathway can exacerbate hepatocyte lipotoxicity (108). Notably, chronic activation of intestine-specific LXRα (rather than hepatic LXRs) has been shown to synergize with a high-cholesterol diet and markedly accelerate the development of MASH-related HCC, highlighting the spatial heterogeneity of LXRs function and an alternative pathway driving carcinogenesis (109). When the disease enters the HCC stage, the function of LXRs changes again and tends to exert tumor inhibition through mechanisms such as reducing intratumoral cholesterol levels, regulating immune microenvironment and inhibiting proliferation-related genes.

LXRs in overlapping etiologies: The functional exhaustion hypothesis. Clinically, CLD often involves overlapping etiologies (e.g., chronic viral hepatitis with concomitant hepatic steatosis), which further complicates the regulation of the LXRs signaling network. In cases of chronic viral hepatitis with hepatic steatosis, viral interference may weaken LXRs-mediated anti-inflammatory and cholesterol-efflux functions, whereas its SREBP-1c-driven lipogenic activity can be amplified, collectively exacerbating intrahepatic lipid accumulation and inflammatory injury (58,110). It is hypothesized that under the long-term combined attack of multiple etiologies, the LXRs pathway may undergo 'functional exhaustion' or 'selective inactivation', that is, its beneficial anti-inflammatory and anti-fibrosis functions are gradually lost and the residual activity of harmful lipid synthesis is exposed, thereby accelerating the evolution to cirrhosis and liver cancer.

In summary, future studies should prioritize the development of complex liver disease models that simulates multi-factor interactions to precisely delineate the LXRs-regulated networks in different etiological combinations and disease stages. Building on such insights, designing cell-or pathway-selective LXRs targeting strategies (e.g., tissue-targeted drugs that selectively activate macrophage LXRs for anti-inflammatory purposes, but simultaneously antagonize the lipid synthesis-promoting effects of hepatocyte

LXRs) has important translational medical significance for restoring its homeostasis regulation function in the context of complex liver diseases and achieving effective and precise intervention.

4. Conclusion

The multiple roles of LXRs make it an important regulator of CLD. Therapeutic targeting of LXRs holds promise for mitigating hepatic steatosis through cholesterol efflux potentiation, suppressing viral replication via lipid raft disruption and restraining HCC progression by modulating oncogenic lipogenesis. However, another feature of LXRs activation is indued lipid production driven by SREBP-1c, which requires precise dose control during LXRs targeted therapy. In order to improve the precision in pharmacological intervention, future strategies should take these aspects into account. Combinatorial regiments: For example, coupling LXRs agonists with SGLT2 inhibitors to counterbalance metabolic side effects. Oltipraz, a drug with anti-fatty degeneration, may be combined with LXRs agonists to counteract the side effects of LXRs activation. In addition, with the discovery of some LXRs modulators, with the support of artificial intelligence and machine learning technology, we should accelerate the discovery and optimization of LXRs modulators. For example, UA, as a natural compound, has demonstrated its potential to inhibit harmful lipid production pathways while retaining beneficial RCT activation. Third, developing tissue-specific LXRβ agonists may avoid LXRα agonists-mediated systemic hypertriglyceridemia. Based on the aforementioned strategies, future research may unlock the full therapeutic potential of LXRs axis in CLD.

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Authors' contributions

HY and XT provided the conceptual idea and design of the present review, wrote the manuscript and contributed equally to this work. XF, JZ, LW, XD and HZ performed the literature search and analysis, were responsible for constructing the figures and tables, and reviewed the manuscript. SL and ML provided valuable guidance and revised the paper. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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