



Review Article

Mechanism of Metabolic Dysfunction-associated Steatotic Liver Disease: Important role of lipid metabolism



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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease, has a high global prevalence and can progress to metabolic dysfunction-associated steatohepatitis, cirrhosis, and hepatocellular carcinoma. The pathogenesis of MASLD is primarily driven by disturbances in hepatic lipid metabolism, involving six key processes: increased hepatic fatty acid uptake, enhanced fatty acid synthesis, reduced oxidative degradation of fatty acids, increased cholesterol uptake, elevated cholesterol synthesis, and increased bile acid synthesis. Consequently, maintaining hepatic lipid metabolic homeostasis is essential for effective MASLD management. Numerous novel molecules and Chinese proprietary medicines have demonstrated promising therapeutic potential in treating MASLD, primarily by inhibiting lipid synthesis and promoting lipid oxidation. In this review, we summarized recent research on MASLD, elucidated the molecular mechanisms by which lipid metabolism disorders contribute to MASLD pathogenesis, and discussed various lipid metabolism-targeted therapeutic approaches for MASLD.

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Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a clinicopathological syndrome characterized by excessive fat deposition in hepatocytes that is not attributable to alcohol or other known liver-damaging factors. In 2023, non-alcoholic fatty liver disease was renamed MASLD following a Delphi consensus process. This renaming emphasizes the importance of metabolism in the disease and provides a

more precise description. Consequently, we use the term MASLD instead of non-alcoholic fatty liver disease. MASLD is an acquired metabolic stress-associated liver injury closely related to insulin resistance and genetic susceptibility. It is one of the most common chronic diseases globally and a significant cause of liver injury in adults. The global prevalence of MASLD is approximately 29.8%.¹ According to the National Health and Nutrition Examination Survey III, the prevalence of MASLD in the United States is 18.8%, rising to 28% in the overweight population.² By 2018, the prevalence of MASLD in China had reached 32.9%, with the total population of MASLD in China expected to increase to 314.58 million people by 2030.³

The development of MASLD is closely linked to genetic alterations and environmental influences. The risk factors can be divided into genetic, epigenetic, and environmental factors.⁴ Genetic factors include mutations in genes such as I148M PNPLA3, TM6SF2, MBOAT7, and GCKR, which increase susceptibility to MASLD.⁵ Epigenetic factors include DNA methylation, chromatin remodeling, and non-coding RNAs. For instance, the M6A "writer" protein methyltransferase-like 3 ameliorates MASLD via RNA methylation.⁶ Additionally, replication protein A1 can maintain lipid metabolism homeostasis and thus ameliorate MASLD by regulating chromatin structure.⁷ Many non-coding RNAs involved in the regulation of lipid metabolism, such as miR-34a, miR-122, and miR-21, play a role in the development of MASLD.⁸ Furthermore, environmental factors play a critical role in the progression of MASLD. These include dietary habits, exercise status, and socioeconomic factors. Unhealthy dietary habits, such as high sugar and fat consumption,⁹ sedentary lifestyles, and infrequent exercise,^{10,11} increase susceptibility to MASLD.

MASLD can be classified as simple steatosis or metabolic dysfunction-associated steatohepatitis (MASH). MASH is characterized by pathological histological lobular inflammation and ballooning of hepatocytes attributable to MASLD. Prolonged liver injury can lead to cirrhosis and hepatocellular carcinoma (HCC). A common clinical method to diagnose MASLD is the detection of hepatic fat density on MRI.¹² Additionally, plasma cytokeratin 18, a marker of hepatocyte apoptosis, has been widely used to assess MASLD.¹³ In recent years, mutations in the PNPLA3 and TM6SF2 genes have been shown to correlate with the severity of MASLD, highlighting their potential as new diagnostic markers. Furthermore, autophagy-related markers, oxidative stress-related markers, inflammatory factors, and liver fibrosis-related markers can also be used to assess the progression of MASLD.

Keywords: MASLD; Lipid metabolism; Cholesterol metabolism; Lipogenesis; Lipolysis; lipid metabolism-targeted drugs; Chinese proprietary medicine.

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Many treatments have been developed for MASLD. First, dietary control and appropriate exercise habits can significantly alleviate MASLD. Second, glucagon-like peptide-1 (GLP-1) agonists, sterol-regulatory element binding protein (SREBP) inhibitors, acetyl-CoA carboxylase (ACC) inhibitors, fatty acid synthase (FASN) inhibitors, stearoyl coenzyme A desaturase (SCD) inhibitors, farnesoid X receptor (FXR) agonists, peroxisome proliferator-activated receptor (PPAR) agonists, and certain natural compounds are considered promising treatments. In recent years, there has been tremendous growth in research focused on treating MASLD by modulating lipid metabolism, with an increasing number of drugs in clinical development. However, the treatment of MASLD remains challenging due to population selection issues and the side effects of current drugs. Given the crucial role of lipid metabolism in MASLD, exploring new drugs and targets for lipid metabolism modulation has become a popular direction for treatment research.

Lipid metabolism

Lipids serve as crucial energy sources in the body, and various molecules involved in lipid metabolism play integral roles in different cellular functions. The development of MASLD is closely related to lipid metabolism, particularly the metabolism of triglycerides and cholesterol. Triglycerides are synthesized from fatty acids. In this review, we primarily focus on fatty acid and cholesterol metabolism. The maintenance of hepatic lipid metabolic homeostasis involves three aspects: uptake, synthesis, and catabolism. It is widely believed that an increase in fatty acid uptake and synthesis or a decrease in lipid degradation leads to the development of MASLD. Therefore, researchers have increasingly focused on these aspects, and various viewpoints have been proposed.

Fatty acid metabolism

Fatty acid intake

The hepatic uptake of fatty acids depends on fatty acid transport carriers, including fatty acid transport proteins (FATPs), cluster of differentiation 36 (CD36), and hepatic caveolin-1 (CAV-1).

FATPs: Six FATP isoforms have been identified, with FATP2 and FATP5 primarily found in the liver.¹⁴ These transport proteins play crucial roles in the development of MASLD. Down-regulation of FATP2 in mice reduces fatty acid uptake and ameliorates hepatic steatosis induced by a high-fat diet.¹⁵ Deletion of FATP2 in the mouse liver alters the metabolic landscape by increasing the expression of PPAR α -regulated genes.¹⁶ Knockdown of FATP5 leads to reduced hepatic fatty acid uptake, which in turn decreases hepatic lipid accumulation.¹⁷ However, decreased hepatic FATP5 expression is associated with the histological progression of MASLD, which might be related to the reduction of hepatic lipid content as MASH advances to cirrhosis.¹⁸ Thus, FATP5 might have a dual role in the development of MASLD.

CD36: Experiments have confirmed the involvement of CD36 in hepatic fatty acid uptake and lipid accumulation.¹⁹ CD36 palmitoylation is an important factor in the pathogenesis of MASLD. *In vitro* and *in vivo* studies have demonstrated that inhibiting CD36 palmitoylation can ameliorate fatty acid metabolism disorders and reduce inflammatory reactions.²⁰ Inhibition of CD36 palmitoylation also attenuates MASLD by promoting CD36 localization to hepatocyte mitochondria.²¹ The palmitoyltransferases DHHC4 and DHHC5 promote fatty acid uptake by targeting CD36.²² Several upstream factors

regulating CD36 are also involved in MASLD. Demethylation of the PPAR γ DNA promoter increases CD36 expression, leading to excessive lipid accumulation.²³ Hepatic Dickkopf-1 enhances fatty acid uptake through the ERK-PPAR γ -CD36 axis.²⁴ Deletion of methyltransferase-like 3 in hepatocytes increases CD36 expression and hepatic free fatty acid uptake, promoting MASH development. Hypoxia-inducible factor 1 α interacts with the CD36 promoter to increase CD36 expression and enhance fatty acid uptake.²⁵ Additionally, non-coding RNAs such as miR-96-5p,²⁶ miR-100,²⁷ miR-26a,²⁸ and miR-195/miR4668²⁹ regulate CD36 expression and affect the development of MASLD.

CAV-1: The role of CAV-1 in the development of MASLD remains controversial due to its role in mediating lipid endocytosis. Although some studies have detected increased CAV-1 expression in the liver tissue of mice with MASLD-fed high-fat diets, others have found a significant reduction in its expression in mice with MASLD.³⁰ Knockdown of CAV-1 in LO2 and AML12 cells resulted in increased steatosis.³¹ CAV-1 upregulation has been found to attenuate lipid accumulation and promote autophagy in mice with MASLD.³² Interestingly, hepatocyte-specific CAV-1 knockdown significantly altered the gene profile in the development of MASLD without affecting hepatic steatosis and fibrosis.³³

De novo fatty acid synthesis

De novo fatty acid synthesis is a process by which the body converts carbon from carbohydrates, such as glucose, and amino acids, including glutamine, into fatty acids. The raw material for *de novo* fatty acid synthesis is acetyl-CoA, which is derived from two sources. First, acetyl-CoA in mitochondria is condensed with oxaloacetate, catalyzed by citrate synthase, to form citric acid, which is then transported to the cytosol by tricarboxylic acid transport proteins in the mitochondrial membrane. Citric acid is subsequently modified by ATP citrate lyase (ACLY) to regenerate acetyl-CoA, which is used for fatty acid synthesis. This process is called the citrate shuttle. Second, acetic acid is linked to coenzyme A to synthesize acetyl-CoA, providing additional raw material for fatty acid synthesis, catalyzed by acetyl-CoA synthetase (ACSS). The generated acetyl-CoA is initially converted to malonyl coenzyme A by ACC, the key rate-limiting step. Malonyl coenzyme A is then converted to palmitic acid *via* FASN. Saturated palmitic acid (FA16:0) can undergo C-chain extension and desaturation by SCD to produce other fatty acid species. These fatty acids can be used to generate more complex lipids. The key enzymes involved in *de novo* fatty acid synthesis play important roles in the development of MASLD (Fig. 1).

SREBPs play critical roles in the development of MASLD by transcriptionally regulating key genes involved in hepatic lipid metabolism. SREBPs are divided into SREBP1 and SREBP2. SREBP1 has two transcripts, SREBP1a and SREBP1c, with SREBP1c being more widely expressed. SREBP1a is expressed in the intestinal epithelium, heart, and macrophages, while SREBP2 is primarily expressed in hepatic and adipose tissue. SREBPs can form trimers with SREBP cleavage-activating protein (SCAP) and INSIG, anchoring the protein in the endoplasmic reticulum (ER). The C-terminal region of SCAP interacts with the C-terminal structural domain of the ER, while the N-terminal region of SCAP contains a sterol-sensing domain sensitive to cholesterol levels. When cholesterol levels are high, SCAP binds with cholesterol and INSIG, resulting in the retention of the entire complex in the ER. Conversely, when cholesterol levels decrease, SCAP does not interact with INSIG, allowing the SREBP-SCAP complex to be internalized into COPII-containing vesicles, which are

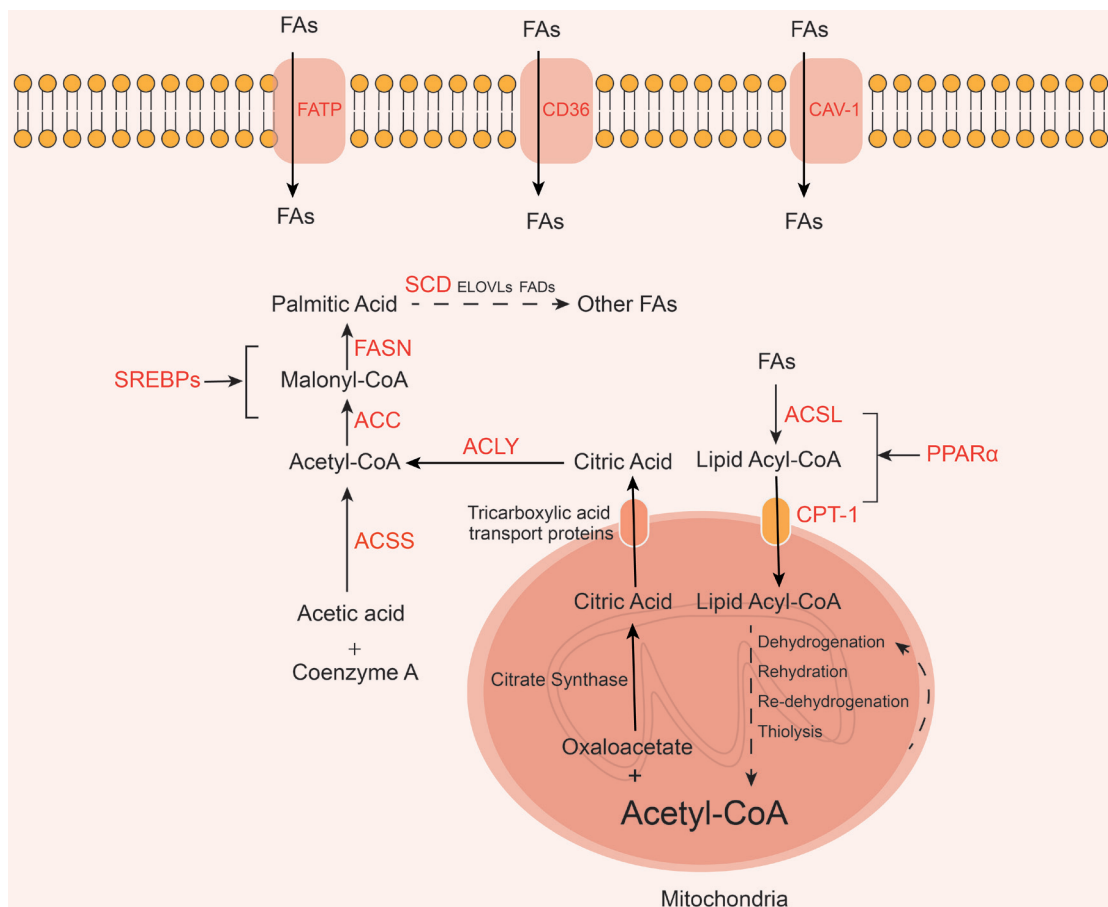


Fig. 1. Fatty acid metabolism. Fatty acid uptake by the liver depends on fatty acid transport carriers, including FATP, CD36, and CAV-1. The raw material for *de novo* fatty acid synthesis is acetyl-CoA, which can be obtained via the citrate shuttle pathway or from acetic acid. ACC and FASN catalyze the conversion of acetyl-CoA into saturated palmitic acid, which can be further modified into other fatty acids by enzymes such as SCD. *De novo* fatty acid synthesis is promoted by SREBPs. Conversely, the β-oxidation of fatty acids occurs in the mitochondria. Fatty acids are converted into fatty acyl-CoA by ACSL and transported via CPT-1 before being oxidized to acetyl-CoA. Fatty acid β-oxidation is promoted by PPARα. FAs, fatty acids; FASN, fatty acid synthase; SREBP, sterol-regulatory element binding protein; FASN, fatty acid synthase; ACC, acetyl-CoA carboxylase; ACLY, ATP citrate lyase; ACSS, acetyl-CoA synthetase; ACSL, acyl-CoA synthetase; PPAR, peroxisome proliferator-activated receptor; CPT-1, carnitine palmitoyltransferase-1.

transported to the Golgi apparatus. Within the Golgi, SREBPs are sequentially cleaved by site-1 protease and site-2 protease, releasing their N-terminal bHLH structural domain into the cytoplasm, where it acts as a transcription factor. The bHLH structural domain migrates to the nucleus, dimerizes, and forms a complex with transcriptional co-activators, activating the transcription of genes with SRE motifs. SREBP1 mainly regulates fatty acid synthesis and LDLR expression, while SREBP2 primarily regulates the expression of cholesterol biosynthetic genes.

ACLY and ACSS: Inhibiting ACLY can reduce hepatic lipid accumulation by suppressing *de novo* fatty acid synthesis. Recent research has clarified the involvement of ACLY in MASLD. In steatotic cells, ACLY mRNA is efficiently translated in a cap-independent manner, promoting adipogenesis.³⁴ The sirtuin 2-ACLY axis is also involved in MASLD progression, with sirtuin 2 inhibiting ACLY and lipid accumulation.³⁵ Additionally, ACLY is degraded by HMG-CoA reductase degradation protein *via* ubiquitination, thereby attenuating MASLD.³⁶ ACSS is involved in the synthesis of acetyl-CoA, which promotes hepatic steatosis. Silencing ACSS2 can effectively inhibit the conversion of fructose to acetyl-CoA and fatty acids in mice.³⁷

ACC: ACC, a key enzyme in *de novo* fatty acid synthesis, plays a significant role in MASLD development. Liver-specific ACC1 knockdown reduces hepatic lipid accumulation and impairs hepatocyte *de novo* fatty acid synthesis in mice.³⁸ AMPK activates the phosphorylation of ACC1 (Ser79Ala) and ACC2 (Ser212Ala), inhibiting the enzymatic activity of ACC and thereby suppressing lipid synthesis. Mutations at these sites are associated with increased *de novo* fatty acid synthesis and steatosis in the liver.³⁹

FASN and SCD: FASN and SCD are markers of lipid synthesis and are both upregulated in MASLD. FASN regulation plays an important role in MASLD. Sorting nexin 8 can prevent MASLD by promoting FASN degradation, making the sorting nexin 8-FASN axis a promising target for MASLD prevention and treatment.⁴⁰ miR-103 can also inhibit hepatic steatosis by targeting FASN and SCD1, which can attenuate MASLD.⁴¹ Slug binds to the FASN promoter, while Slug-associated LSD1 catalyzes H3K9 demethylation, stimulating FASN expression and lipogenesis.⁴² Furthermore, in MASLD, the levels of mitochondrial pyruvate carrier 1 are positively correlated with hepatic lipid deposition, and mitochondrial pyruvate carrier 1 knockdown affects FASN lactylation at K673, ultimately inhibiting FASN activity.⁴³

SREBP1: SREBP1c induces the expression of ACC, FASN, and SCD, promoting hepatic fatty acid and triglyceride synthesis. Increased SREBP1 expression is observed in patients with MASLD, and SREBP1c overexpression in mice increases hepatic triglyceride levels.⁴⁴ However, exercise and strength training can reduce hepatic lipid accumulation by down-regulating SREBP1.^{45,46} Activated AMPK phosphorylates SREBPs, reducing their activity and inhibiting hepatic lipid accumulation. VEGFB,⁴⁷ MD2,⁴⁸ and protectin DX⁴⁹ are involved in MASLD development through the AMPK–SREBP1 pathway. mTOR promotes the maturation and nucleation of SREBP1, enhancing lipid synthesis.⁵⁰ Pancreatic progenitor cell differentiation and proliferation factor reduces hepatic steatosis by inhibiting mTOR/SPRBP1.⁵¹ CD36 promotes *de novo* lipogenesis through INSIG2-dependent SREBP1 hydrolytic processing.⁵² Additionally, non-coding RNAs including miR-23a/b-3p,⁵³ miR-33-5p,⁵⁴ and miR-130b-5p⁵⁵ regulate SREBP1 expression. ZBTB7A,⁵⁶ ceramide synthase,⁵⁷ and dihydroxytryptamine⁵⁸ are believed to upregulate SREBP1, promoting lipid synthesis. Interestingly, although SREBP1a does not contribute to hepatic lipogenesis, its absence in hepatocytes or macrophages exacerbates methionine- and choline-deficient diet-induced MASLD.⁵⁹

SREBP2: The high-fat, choline-deficient, amino acid-defined diet model is a newly established mouse model of MASH that activates the SREBP2/SCD2 gene and drives liver fibrosis through high-fat feeding.⁶⁰ The expression of SCD, FASN, and SREBP2 is increased in rats fed a Western diet.⁶¹ Moreover, SREBP2 is regulated by the AMPK signaling pathway, and increased expression of SREBP2 alleviates autophagic dysfunction in MASLD.⁶²

Fatty acid β -oxidation

Fatty acid oxidation refers to the process by which fatty acids are degraded in the presence of oxygen to release energy for various biological processes. The most common pathway is the β -oxidation of fatty acids. β -oxidation of long-chain fatty acids occurs in the mitochondria, whereas very-long-chain fatty acids are oxidized in peroxisomes. Mitochondrial β -oxidation consists of three steps. First, fatty acids are activated to fatty acyl-CoA, a reaction catalyzed by acyl-CoA synthetase (ACSL). Second, while the enzyme system catalyzing fatty acid β -oxidation is located in the mitochondrial matrix, long-chain fatty acyl-CoA requires a carrier, namely carnitine palmitoyltransferase-1 (CPT-1), to be transported through the inner mitochondrial membrane. Finally, the β -oxidation of fatty acyl-CoA in the mitochondrial matrix proceeds through a four-step reaction involving dehydrogenation, hydration, re-dehydrogenation, and thiolysis, ultimately producing one molecule of acetyl-CoA and a new molecule of fatty acyl-CoA with two fewer carbons. This cycle repeats several times to gradually produce more acetyl-CoA. Peroxisomal β -oxidation is similar to mitochondrial β -oxidation, but the first step is catalyzed by lipid acyl-CoA oxidase (Fig. 1).

The PPAR system, particularly PPAR α , plays an important role in the regulation of lipid metabolism. Activated PPARs form heterodimers with the retinoid X receptor and bind to peroxisome proliferator-responsive elements upstream of certain genes to activate enzymes related to lipid metabolism. PPAR α has various roles in lipid metabolism, including promoting fatty acid β -oxidation and inhibiting MASLD development.

ACSL: TANK-binding kinase 1 acts as a scaffolding protein to localize ACSL1 to mitochondria and promote fatty acid oxidation.⁶³ Although ACSL4 is weakly expressed in the liver, it is upregulated in patients with MASLD, which contradicts the conventional belief that ACSL4 promotes fatty acid

β -oxidation and inhibits MASLD.⁶⁴ This might be attributable to ACSL4's ability to promote inflammation⁶⁵ and its involvement in ferroptosis.⁶⁶ Additionally, P115 interacts with ACSL4 and degrades it. P115 is significantly upregulated in the livers of high-fat diet-fed mice, resulting in the downregulation of ACSL4 protein.⁶⁷ ACSL5 knockdown in mice increases energy expenditure and insulin sensitivity and delays fat absorption.⁶⁸

CPT-1: Exercise can lead to CPT-1 downregulation, thereby reducing the disruption of lipid metabolism in MASLD.^{69,70}

PPAR α : Metabolomic and lipidomic screening revealed that PPAR α plays an important role in the progression of MASH to HCC.⁷¹ In a mouse model, obese female offspring fed a high-fat diet exhibited impaired hepatic PPAR α activation.⁷² Moreover, PPAR α is sex-selective, making male mice more susceptible to MASLD.⁷³ Mechanistically, PPAR α can reduce hepatic steatosis by rebuilding the intestinal barrier and regulating the distribution of the intestinal flora.⁷⁴ Intestinal PPAR α in mice with MASLD can promote MASH progression by regulating fatty acid uptake.⁷⁵ Several molecules can also affect MASLD by influencing PPAR α . For example, the anti-adipogenic factor coenzyme Q10 regulates MASLD by upregulating PPAR α and CPT-1.⁷⁶ Programmed cell death 4,⁷⁷ obesity-associated protein,⁷⁸ and mothers against decapentaplegic homolog family member 4⁷⁹ promote hepatocyte lipid deposition by inhibiting PPAR α -mediated fatty acid oxidation.

Cholesterol metabolism

Cholesterol uptake

The uptake of dietary cholesterol by intestinal epithelial cells is facilitated by Niemann–Pick type C1-like 1 (NPC1L1). The accumulated cholesterol is then esterified by cholesterol acyltransferases, also known as sterol O-acyltransferases, for hepatic uptake.⁸⁰

NPC1L1: Expression of the human NPC1L1 gene in the mouse liver exacerbates high-fat diet-induced steatosis.^{81,82}

Cholesterol synthesis

Cholesterol synthesis originates from acetyl-CoA through a complex process involving nearly 30 enzymatic steps. This process can be roughly divided into three stages: synthesis of isopentenyl pyrophosphate from acetyl-CoA, synthesis of squalene, and conversion of squalene to cholesterol (Fig. 2). The key enzymes involved in this process are mammalian 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase (HMGCR/HMGR) and squalene monooxygenase (SM/SQLE). HMGCR catalyzes the conversion of HMG-CoA to mevalonate in the first phase, while squalene is oxidized by SM in the third stage to produce 2,3-oxidized squalene, a precursor of cholesterol and sterols.

HMGCR: Dysregulated cholesterol metabolism can exacerbate MASLD. The development of MASLD is associated with increased HMGCR expression and reduced HMGCR phosphorylation.⁸³ A genomic analysis of a high-fat-fed mouse model of MASLD showed a 2.06-fold upregulation of HMGCR.⁸⁴ HMGCR is regulated by Dicer1/miR-29, indicating that the Dicer1–miR-29–HMGCR axis is involved in free cholesterol accumulation in the livers of mice with MASLD.⁸⁵

SM/SQLE: SM/SQLE is implicated in the progression of MASLD to HCC. It is the most significantly overexpressed metabolic gene in patients with MASLD and HCC, and its expression accelerates the development of HCC induced by a high-fat, high-cholesterol diet in mice.^{86–88} The underlying mechanisms include the promotion of MASH and HCC development through the induction of cholesterol biosynthesis, the SQLE–CA3 axis-mediated lipogenesis,⁸⁸ and P53-mediated

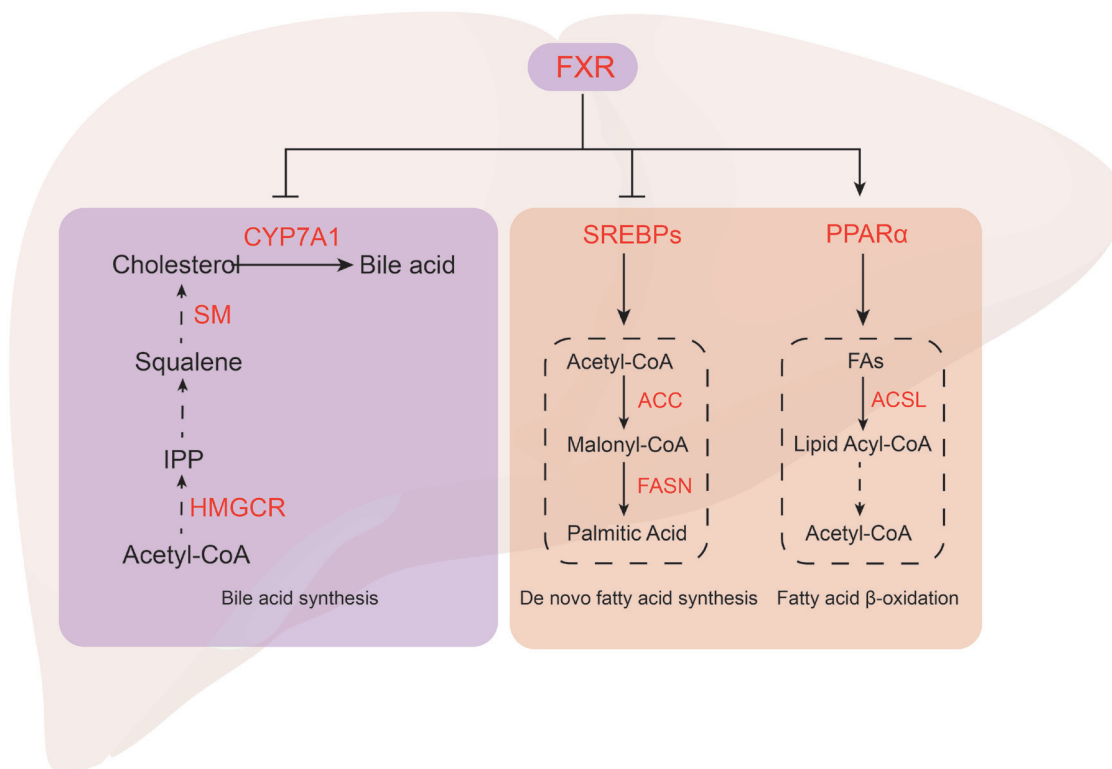


Fig. 2. Cholesterol metabolism. The process of cholesterol synthesis is complex and can be roughly divided into three stages: synthesis of IPP from acetyl-CoA, synthesis of squalene, and conversion of squalene to cholesterol. HMGCR and SM are the key enzymes in cholesterol synthesis. The primary route of cholesterol production is bile acid synthesis catalyzed by CYP7A1. FXR is an important regulator of cholesterol metabolism; its activation inhibits CYP7A1, leading to the inhibition of bile acid synthesis. FXR, farnesoid X receptor; CYP7A1, cholesterol 7 α -hydroxylase; SM, squalene monooxygenase; HMGCR, 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase; IPP, isopentenyl pyrophosphate; SREBP, sterol-regulatory element binding protein; PPAR α , peroxisome proliferator-activated receptor; FAs, fatty acids; ACC, acetyl-CoA carboxylase; FASN, fatty acid synthase; ACLY, ATP citrate lyase.

ed transcriptional regulation of SQLE to suppress cholesterol synthesis and tumor growth.⁸⁹

Bile acid synthesis

Bile-acid synthesis is the primary pathway for cholesterol catabolism, and the key enzyme in this process is cholesterol 7 α -hydroxylase (CYP7A1). Patients with MASLD often exhibit disordered bile acid metabolism. Hepatic bile acid synthesis is mainly regulated by FXR, and FXR activation inhibits *de novo* bile acid synthesis (Fig. 2).

CYP7A1: Bioinformatic analysis has revealed that CYP7A1 is involved in the development of MASLD, MASH, and HCC.^{90,91} In MASLD, CYP7A1 mRNA expression is increased.⁹² However, CYP7A1 mRNA levels decline with the progression of MASH-associated liver fibrosis.⁹³

FXR: FXR plays a crucial role in the development of MASLD. On one hand, FXR activation promotes the production of short heterodimer partner, which downregulates the rate-limiting enzyme CYP7A1, ultimately inhibiting bile acid synthesis. Studies have demonstrated that FXR activation can prevent MASLD by reducing lipid uptake in a bile acid-dependent manner.⁹⁴ On the other hand, FXR activation decreases hepatic lipid accumulation by inhibiting triglyceride synthesis, achieved through the induction of short heterodimer partner expression and the downregulation of SREBP1 and FASN.

FXR deficiency in mice results in hepatic steatosis, lipid droplet accumulation in hepatocytes, disturbed glucose metabolism, and elevated blood lipid levels.⁹⁵ FXR functions as a nuclear transcription factor that regulates glucose and li-

pid metabolic homeostasis through pyruvate dehydrogenase kinase 4.⁹⁵ Furthermore, FXR sulfation, a post-translational modification influenced by endogenous hepatic cystathionine γ lyase/hydrogen sulfide, promotes FXR activity, thereby improving MASLD.⁹⁶ MiR-552-3p ameliorates hepatic lipid metabolism disorders by regulating the transcriptional activity of FXR.⁹⁷

Drugs that treat MASLD by regulating lipid metabolism

The FDA has approved Rezdiffra (resmetirom), a thyroid hormone receptor β -1 agonist, as the first treatment for MASH. Resmetirom selectively activates thyroid hormone receptor β -1, resulting in a reduction of free thyroxine (T4) levels by approximately 16–19%. Notably, it does not influence the levels of thyrotropin or free triiodothyronine.⁹⁸ Resmetirom also significantly reduces cholesterol and triglyceride levels and enhances fatty acid oxidation, demonstrating substantial potential for the treatment of MASLD. Meanwhile, there has been increasing interest in developing new drugs for MASLD treatment. In this section, we review recent articles exploring molecular drugs and Chinese proprietary medicines (CPMs) that inhibit MASLD. Most of these drugs/CPMs work by inhibiting fatty acid uptake and synthesis while promoting fatty acid oxidation. Similarly, the inhibition of cholesterol uptake and synthesis, as well as bile acid synthesis, can also be used to improve MASLD. CPMs have shown great potential in MASLD treatment. The modification of inhibitors and activators targeting key regulatory genes, such as GLP-1, SREBP, ACC,

Table 1. Clinical trials of GLP-1 agonists

Drugs	Conclusions	Phase	References
Dulaglutide	Improvement in patients with type 2 diabetes and MASLD	\	114
Efinopegdutide	Improvement of MASH and MASLD	Phase II	107
Exenatide	Improvement in patients with type 2 diabetes and MASLD	\	115
Liraglutide	Improvement of MASH and MASLD	Phase II/III	116–118
	Improvement in patients with type 2 diabetes and MASLD	Phase IV	119
	No improvement in patients with type 2 diabetes and MASLD	Phase IV	120
Semaglutide	Improvement of MASH but not liver fibrosis	Phase I/II	121,122
	Improvement of health-related quality of life in patients with MASH and liver fibrosis	Phase II	103

MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis.

FASN, SCD1, PPAR α , and FXR, has gained increasing attention in recent years. Improving the therapeutic efficacy of drugs and reducing their potential side effects have become major research goals in this field.

GLP-1 agonists: GLP-1 regulates insulin and glucagon secretion and modulates intestinal motility, and its agonists have been considered promising therapeutics in recent years for reducing the risk of MASLD and its associated mortality.⁹⁹ GLP-1 agonists, such as semaglutide and liraglutide, effectively treat MASLD by reducing visceral and hepatic fat content.^{100–102} Semaglutide improves the health-related quality of life in patients with MASLD,¹⁰³ with daily dosing proving more effective.¹⁰⁴ Mechanistically, semaglutide induces modifications in the gut microbiota and ameliorates MASLD.¹⁰⁵ Dual GLP-1/GLP-2 receptor agonists,¹⁰⁶ as well as dual GLP-1 receptor/glucagon receptor agonists like ALT-801, NN1177, and efinopegdutide,^{107–109} have shown good therapeutic efficacy in MASLD. The combination of GLP-1 activators with other drugs is also the focus of an increasing number of studies. Combined treatment with semaglutide and the FXR agonist cilofexor, the ACC inhibitor firsocostat, and the ACLY inhibitor has demonstrated better therapeutic efficacy than monotherapy.^{110,111} Novel GLP-1 activators, such as cincholine and exendin-4, are also under development.^{112,113}

The findings of clinical trials on GLP-1 agonists are listed in Table 1.^{103,107,114–122} “\” indicates that no phasing information for the clinical trial could be found.

SREBP inhibitors: Betulin is a specific inhibitor of SREBP maturation. It inhibits the transport of SREBP to the Golgi via SCAP,⁵² thereby inhibiting the processes of fatty acid and cholesterol synthesis. Betulin has shown potential in the treatment of MASLD.^{123–126} PF-429242 is a specific inhibitor of the proteasome site-1 protease, which inhibits the cleavage and release of the SREBP precursor protein. It is also considered to have potential in MASLD control.¹²⁷

ACC inhibitors: ACC inhibition reduces lipid accumulation in hepatocytes and inhibits pro-fibrosis activity in liver stem cells, suggesting that small-molecule inhibitors of ACC can attenuate liver fibrosis by reducing hepatocyte lipotoxicity and preventing liver stem cell activation. These findings provide a mechanistic basis for the treatment of patients with MASH and advanced liver fibrosis.¹²⁸ However, while ACC inhibitors have been found to reverse MASLD, they may also promote hypertriglyceridemia.¹²⁹ GS-0976 (Firsocostat) has shown promise in alleviating MASH in Phase II clinical trials.^{130,131} However, firsocostat can cause hyperlipidemia, which can be alleviated by fenofibrate.^{132,133} The ACC inhibitor ND-654, which mimics the action of ACC phosphorylation, inhibits hepatic de novo fatty acid synthesis.³⁹ In mouse

models, treatment with selective ACC1 inhibitors significantly ameliorated hepatic steatosis and liver fibrosis, supporting their use as new therapies for MASLD/MASH.¹³⁴ Additionally, both the dual ACC1/ACC2 inhibitor PF-05221304¹³⁵ and the novel ACC1/ACC2 inhibitor WZ66¹³⁶ have been shown to alleviate MASH in mouse models.

FASN or SCD1 inhibitors: In patients with MASLD, FASN inhibitors such as TVB-2640 (Denifanstat)¹³⁷ and FT-4101¹³⁸ reduce hepatic *de novo* lipogenesis and steatosis. FASStatin may be useful in treating MASLD by targeting and degrading FASN.¹³⁹ Both the SCD1 inhibitor CAY10566 and a novel SCD1 inhibitor have inhibited hepatic lipid accumulation in mice, suggesting that SCD1 may be an effective target for the treatment of MASLD.^{140,141}

PPAR agonists: Fibrates are clinically available PPAR α agonists for MASLD treatment. The literature indicates that PPAR α -mediated peroxisome adaptation is crucial for fenofibrate-mediated improvements in MASLD.¹⁴² Combining PPAR α with other dual-receptor agonists has shown great potential in MASLD treatment. The novel PPAR α / γ agonists G4 and G5 effectively inhibited hepatic steatosis while avoiding the side effects of pioglitazone.¹⁴³ The PPAR α / γ agonist aleglitazar significantly reduced hepatic steatosis and fibrosis.¹⁴⁴ The PPAR α / δ agonist compound H11, which exhibits effective and balanced PPAR α / δ agonist activity, has shown promise in MASH treatment.¹⁴⁵ Additionally, ZLY18, a quadruple free fatty acid receptor 1 and PPAR α / γ / δ agonist, might be a highly effective anti-MASLD drug.¹⁴⁶

The findings of the clinical trials on PPAR agonists are listed in Table 2.^{144,147–150} “\” indicates that no phasing information for the clinical trial could be found.

FXR agonists: Although traditional FXR agonists have been used in the clinic, their side effects have limited their application to some extent. The traditional FXR agonist, obeticholic acid, has been abandoned for MASLD treatment. New FXR agonists, such as nidufexor (LMB763),¹⁵¹ cilofexor,¹⁵² and EDP-305,¹⁵³ have entered clinical trials for the treatment of MASLD or MASH. In recent years, the development of FXR agonists with stronger activity and fewer side effects has received increasing attention. For instance, 1-adamantylcarbonyl-4-phenylpiperazine is an FXR agonist, and its derivative compound 10A was found to be more effective in ameliorating hyperlipidemia, hepatic steatosis, and insulin resistance.¹⁵⁴ Additionally, structural optimization of non-bile acid FXR agonists led to the development of compound 42 as an FXR agonist with high efficiency and selectivity for alleviating MASH.¹⁵⁵ MET409, an FXR agonist with a unique chemical structure, significantly suppressed hepatic fat content without causing significant or severe

Table 2. Clinical trials of PPAR agonists

Drugs	Targets	Conclusions	Phase	References
Aleglitazar	PPAR α / γ	Improvement of MASLD and liver fibrosis	\	144
Elafibranor	PPAR α / δ	Improvement of MASH	Phase II	147
Lanifibranor	Pan-PPAR	Improvement of MASH and liver fibrosis	Phase III	148
Saroglitazar	PPAR α / γ	Improvement of MASH and MASLD	Phase II	149,150

PPAR, peroxisome proliferator-activated receptor; MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis.

Table 3. Clinical trials of FXR agonists

Drugs	Conclusions	Phase	References
Cilofexor	Improvement of MASH	Phase II	152,159
MET409	Improvement of MASH	Phase I	156
Obeticholic acid	Improvement in patients with type 2 diabetes and MASH	Phase II	160
Tropifexor	Improvement of MASH	Phase II	161
Vonafexor	Improvement of liver and kidney function in patients with MASH and liver fibrosis	Phase II	162

MASH, metabolic dysfunction-associated steatohepatitis.

side effects in patients with MASH.¹⁵⁶ Moreover, tissue-selective FXR agonists have been studied. For example, (E)-3-(3-((2-cyano-4'-dimethylaminobiphenyl-4-ylmethyl)cyclohexanecarbonylamino)-5-fluorophenyl) acrylic acid methyl ester is an entero-selective FXR partial agonist that significantly reduced the extent of liver fibrosis and decreased the levels of fibrosis markers and serum AST.¹⁵⁷ BMS-986339 exhibited potent FXR activation and anti-fibrotic efficacy despite its tissue selectivity, reducing the activation of certain

genes in the liver.¹⁵⁸

The findings of the clinical trials on FXR agonists are listed in Table 3.^{152,156,159-162}

Natural compounds: Many natural compounds, including CPMs, are considered promising in the treatment of MASLD. Recent studies on natural compounds and their molecular mechanisms are listed in Table 4.¹⁶³⁻¹⁸⁷ However, the use of many CPMs for the treatment of MASLD still needs to be tested in rigorous clinical trials. Nevertheless, CPMs remain

Table 4. Drugs that treat MASLD by regulating lipid metabolism

Drugs	Mechanism	References
Andrographolide	Inhibits FATP2	163
Baicalein	Inhibits fatty acid synthesis; promotes fatty acid oxidation; activates AMPK; inhibits SREBP1	164,165
Berberine/oxyberberine	Inhibits fatty acid synthesis; promotes fatty acid oxidation; regulates SIRT3/AMPK/ACC; downregulates SIRT1/FoxO1/SREBP2; inhibits cholesterol synthesis	166-170
Curcumin	Inhibits CD36, SLC13A5, and ACLY; regulates CYP2E1, SREBP1c, and PPAR α	171-173
Extract of <i>Dillenia indica</i> L.	Regulates SIRT1/pLKB1/AMPK, HMGCR, and PPAR α signaling pathways	174
Extract of <i>Liriope platyphylla</i>	Inhibits fatty acid uptake and synthesis	175
Extract of root from <i>Arctium lappa</i> L.	Activates AMPK/ACC/CPT1	176
Jian Pi Qing Gan Yin decoction	Activates AMPK/PPAR α ; inhibits LXRA/SREBP1/NF- κ B	177
Kangtaizhi Granule	Regulates PPAR γ , SREBP1, pAKT, FAS, and SIRT1	178
Limonin	AMPK agonist; downregulates FASN and SREBP1	179,180
Naringenin	Activates the CaMKK β /AMPK/ACC pathway	181
Paeoniflorin	Activates LKB1/AMPK and PPAR α	182,183
Puerarin	Inhibits fatty acid uptake and synthesis; promotes fatty acid oxidation; inhibits FASN, SREBP1c; activates AMPK	184,185
Saikosaponin	Inhibits SREBP1c; activates PPAR α ; inhibits FASN; promotes ACOX1 and CPT1	186,187

FATP, fatty acid transport protein; AMPK, AMP-activated protein kinase; SREBP, sterol regulatory element-binding protein; ACC, acetyl-CoA carboxylase; ACLY, ATP citrate lyase; PPAR, peroxisome proliferator-activated receptor; HMGCR, 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase; CPT1, carnitine palmitoyltransferase-1; FASN, fatty acid synthase.

a valuable resource in modern medicine and have significant potential for the future treatment of MASLD.

Discussion

MASLD represents a continuum of liver diseases that includes simple steatosis and metabolic dysfunction-associated steatohepatitis. The global prevalence of MASLD is estimated to be as high as 29.8%, making it one of the most significant diseases. Most patients with MASLD are asymptomatic and only present with incidental findings of hepatomegaly or slight-to-moderate increases in ALT and AST levels during routine physical examinations. The current primary approach for treating MASLD is reducing hepatic steatosis by regulating lipid metabolism. Dietary control and appropriate exercise can significantly improve the symptoms of MASLD. Additionally, drugs such as FXR agonists, PPAR α agonists, and SREBP1 inhibitors have been explored for MASLD treatment because of their ability to regulate lipid metabolism.

The pathology of MASLD is characterized by hepatic steatosis, the development of which is mainly related to dysregulated hepatic lipid metabolism. The development of MASLD is generally attributed to six factors: increased hepatic fatty acid uptake and synthesis, decreased fat oxidation, increased cholesterol uptake and synthesis, and increased bile acid synthesis. (1) Regarding increased fatty acid uptake, FATP and CD36 are upregulated in MASLD. Although CAV-1 is involved in fat uptake, its role in MASLD remains controversial. (2) Concerning increased *de novo* lipogenesis, ACLY, ACSS, ACC, FASN, and SCD, key enzymes involved in *de novo* fatty acid synthesis, are upregulated in MASLD. Among them, SREBP1 can sense cholesterol levels and affect MASLD by transcriptionally regulating key genes involved in hepatic lipid metabolism. SREBP1 induces ACC, FASN, SCD, and other lipid synthesis genes to promote hepatic fatty acid and triglyceride synthesis. SREBP1 has been considered to have great potential as a treatment target for MASLD. (3) Inhibition of fatty acid oxidation can also lead to MASLD. Inhibition of ACSL and CPT-1, key enzymes in lipolysis, can exacerbate hepatic steatosis. Fatty acid oxidation can be regulated by PPAR α , and PPAR α activation promotes CPT1 expression, thereby enhancing fatty acid β -oxidation. Dysregulated cholesterol metabolism is also involved in the development of MASLD. (4) Increased cholesterol uptake can exacerbate MASLD through increased NPC1L1 expression. (5) Regarding increased cholesterol synthesis, HMGCR, a key enzyme for cholesterol synthesis, is upregulated in MASLD. SM has also been found to play an important role in the progression of MASLD to HCC. (6) Finally, increased bile acid synthesis is involved in the development of MASLD. CYP7A1, a key enzyme involved in bile acid synthesis, has elevated expression in MASLD. Hepatic bile acid synthesis is mainly regulated by FXR, and FXR activation inhibits *de novo* bile acid synthesis, thereby ameliorating MASLD.

Conclusions

Although much research has investigated the mechanisms of MASLD development, some unanswered questions remain. Peroxisomes are involved in the β -oxidation of extra-long-chain fatty acids, but little research has assessed the connection between peroxisomes and MASLD. Current models of MASLD are mainly based on oleic acid-induced cells and high-fat diet-fed mice, which do not fully capture the dynamic process of MASH fibrosis that can progress to cirrhosis and HCC. Thus, the need for novel, low-cost, and rapid MASLD models for life science research is evident. Despite numerous new drugs, including molecule drugs and CPMs, enter-

ing clinical trials in recent years, the treatment of MASLD remains ineffective given the large MASLD population. Lipid metabolism, as an important mechanism in the development of MASLD, has been the primary focus of MASLD treatment. Therefore, the exploration of new drugs and targets that regulate lipid metabolism for MASLD treatment is an area that requires in-depth research.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

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