



Review Article



Orphan Nuclear Receptors in Metabolic Dysfunction-associated Steatotic Liver Disease Development

Huan Li[#], Jian Chen[#], Ziyin Huang and Mingkai Chen^{* ID}

Department of Gastroenterology, Renmin Hospital of Wuhan University, Wuhan, Hubei, China

Received: January 09, 2025 | Revised: May 09, 2025 | Accepted: May 19, 2025 | Published online: June 19, 2025

Abstract

Metabolic dysfunction-associated fatty liver disease, representing a spectrum of liver disorders from simple steatosis to metabolic dysfunction-associated steatohepatitis, fibrosis, and cirrhosis, has emerged as one of the most prevalent chronic liver conditions globally, affecting an estimated approximately 30% of the world's population. Its pathogenesis is highly complex, involving intricate interactions between genetic predisposition, metabolic dysregulation, inflammation, and cellular stress responses. Within this complex landscape, orphan nuclear receptors (ONRs) have gained significant attention. Defined by the lack of identified endogenous ligands, ONRs function as master transcriptional regulators controlling diverse biological processes. Crucially, they play pivotal roles in the development and progression of numerous diseases, including metabolic disorders. This review specifically focuses on elucidating the critical contributions of various ONRs to the pathogenesis of metabolic dysfunction-associated fatty liver disease. We examined how these receptors modulate key pathological drivers: lipid metabolism, inflammation, and autophagy.

Citation of this article: Li H, Chen J, Huang Z, Chen M. Orphan Nuclear Receptors in Metabolic Dysfunction-associated Steatotic Liver Disease Development. J Clin Transl Hepatol 2025. doi: 10.14218/JCTH.2025.00019.

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as one of the most prevalent chronic liver conditions worldwide, affecting approximately 30% of the global population.¹ MASLD encompasses metabolic dysfunction-associated steatotic liver and metabolic dysfunction-associated steatohepatitis (MASH), including their associated fibrotic stages.² Research has established a strong correlation between MASLD and systemic metabolic disorders such as obesity, insulin resistance, and type 2 diabetes, indicating that this condition is not merely a localized hepatic pathology

but rather a multisystem disease intricately linked to systemic metabolic dysregulation.³

Orphan nuclear receptors, one of the three major subfamilies of nuclear receptors, lack identified endogenous ligands. Among the 48 known nuclear receptors, 25 are classified as orphan nuclear receptors. They function as transcription factors or cofactors, regulating gene transcription and participating in various metabolic processes.⁴ A summary of orphan nuclear receptors is provided in Table 1.⁵⁻³⁹ As core regulators of metabolic homeostasis, orphan nuclear receptors contribute to MASLD pathogenesis. For instance, chicken ovalbumin upstream promoter-transcription factor II (also known as NR2F2) is upregulated in fibrotic kidneys and livers in humans, and overexpression of NR2F2 inhibits the fatty acid oxidation pathway in fibroblasts.⁴⁰ During fasting, estrogen-related receptor (ERR) γ (also known as NR3B3) undergoes O-GlcNAcylation by O-GlcNAc transferase, which increases its stability and enhances its recruitment to gluconeogenic gene promoters, thereby upregulating gluconeogenic gene expression in the liver.⁴¹ Small heterodimer partner (SHP, also known as NR0B2) inhibits the conversion of cholesterol to bile acids and plays a key role in maintaining cholesterol and bile acid homeostasis.⁴² The farnesoid X receptor (FXR) agonist GSK2324 reduces hepatic fatty acid uptake and synthesis to control liver lipid levels, while bile acid supplementation reverses this effect, suggesting that bile acid metabolism plays a critical role in hepatic lipid metabolism.⁴³ Emerging evidence demonstrates that orphan nuclear receptors exert pleiotropic effects on MASLD progression through distinct yet interconnected mechanisms involving metabolic regulation, inflammation suppression, and fibrogenesis inhibition. However, systematic investigations remain limited, preventing comprehensive delineation of their integrative roles within the lipid metabolism-inflammation-fibrosis axis of MASLD pathogenesis.

Therefore, this article reviews the roles of orphan nuclear receptors in MASLD, aiming to elucidate their multidimensional regulatory characteristics, highlight their potential as novel therapeutic targets, and provide directions for future research.

NRO

The orphan nuclear receptor NR0 family consists of two members, NR0B1 (DAX-1) and NR0B2 (SHP). Both receptors lack the canonical DNA-binding domain and thus cannot directly regulate transcription. Instead, they function as coactivators or corepressors to modulate cellular activi-

Keywords: Metabolic dysfunction-associated steatotic liver disease; MASLD; Orphan nuclear receptors; ONRs; SHP; RORs; HNF4 α ; ERRs; LRH-1.

[#]Contributed equally to the study.

***Correspondence to:** Mingkai Chen, Department of Gastroenterology, Renmin Hospital of Wuhan University, Wuhan, Hubei 430060, China. ORCID: <https://orcid.org/0000-0003-3652-6863>. Tel: +86-13720330580, Fax: +86-27-88042292. E-mail: kaimingchen@163.com.

Table 1. Information on orphan nuclear receptors

Gene	Common name	Full name	Function on MASLD
NR0B1	DAX-1	Dosage-sensitive sex reversal	Not or very lowly expressed
NR0B2	SHP	Small heterodimer partner	Inhibit fat synthesis, ⁵⁻⁷ alleviate inflammation and fibrosis, ^{8,9} and participate in the circadian rhythm regulation of the liver ¹⁰
NR1D1	REV-ERB α	Reverse strand of ERB-alpha	Inhibit fat synthesis, ¹¹ alleviate inflammation and fibrosis, ¹² and participate in the circadian rhythm regulation of the liver ^{17,18}
NR1D2	REV-ERB β	Reverse strand of ERB-beta	Not or very lowly expressed
NR1F1	ROR α	Retinoid-related orphan nuclear receptor-alpha	Promote fat breakdown and lipophagy, ^{13,14} influence mitochondrial quality, ¹⁵ and participate in the circadian rhythm regulation of the liver ¹⁸
NR1F2	ROR β	Retinoid-related orphan nuclear receptor-beta	Not or very lowly expressed
NR1F3	ROR γ	Retinoid-related orphan nuclear receptor-gamma	Increase fat accumulation, ¹⁶ and participate in the circadian rhythm regulation of the liver ¹⁹
NR2A1	HNF4 α	Hepatocyte nuclear factor 4-alpha	Increase fatty acid oxidation and lipophagy, ^{20,21} reduce fat synthesis, ²² participate in lipid transport, ²³ and promote bile acid uptake and synthesis ²⁴
NR2A2	HNF4 γ	Hepatocyte nuclear factor 4-gamma	Not or very lowly expressed
NR2C1	TR2	Testicular nuclear receptors 2	Not or very lowly expressed
NR2C2	TR4	Testicular nuclear receptors 4	Not or very lowly expressed
NR2E1	TLX	Nuclear receptor tailless	Promote cholesterol and fatty acid synthesis while inhibiting fatty acid oxidation ²⁵
NR2E3	PNR	Photoreceptor-specific nuclear receptor	Not or very lowly expressed
NR2F1	COUP-TFI	Chick ovalbumin upstream promoter-transcription factor-1	Not or very lowly expressed
NR2F2	COUP-TF-II	Chick ovalbumin upstream promoter-transcription factor-2	Increase fat accumulation and promote hepatic stellate cell activation ²⁶
NR2F6	EAR2	V-erb-related gene	Increase hepatic uptake of free fatty acids ²⁷
NR3B1	ERR α	Estrogen-related receptor alpha	Promote fat synthesis ²⁹ and insulin resistance, ³⁰ inhibit autophagy activity ³¹ and fat transport ³²
NR3B2	ERR β	Estrogen-related receptor beta	Not or very lowly expressed
NR3B3	ERR γ	Estrogen-related receptor gamma	Promote fat synthesis ²⁸
NR4A1	Nur77	Nerve growth factor-1 β	Inhibit liver inflammation, ³³ regulate mitochondrial function ³⁴
	TR3		
	NGFIB		
NR4A2	Nurr1	Nuclear receptor related-1	Involved in fat degeneration, ³⁵ liver extracellular matrix formation ³⁶
	RNR-1		
	TONOR		
NR4A3	Nor1	Neuron-derived orphan receptor-1	Not or very lowly expressed
NR5A1	SF-1	Steroidogenic factor-1	Not or very lowly expressed
NR5A2	LRH-1	Liver receptor homolog-1	Involved in liver lipid accumulation and phospholipid composition, ^{37,38} reduce liver oxidative stress ³⁹
NR6A1	GCNF	Germ cell nuclear factor	Not or very lowly expressed

MASLD, metabolic dysfunction-associated steatotic liver disease; TG, triglycerides; KO, knockout; ROS, reactive oxygen species.

ties.⁴ SHP is an inhibitory nuclear receptor primarily expressed in the liver, heart, pancreas, skeletal muscle, and adipose tissue. It plays a crucial role in regulating cholesterol metabolism, energy homeostasis, and bile acid metabolism.⁴⁴ Studies have shown that increased SHP expression can alleviate liver lipid accumulation in mice subjected to a high-fat diet (HFD).⁴⁵ Notably, a point mutation introducing T58A (ACC to GCA) in SHP (NM_011850.3) causes SHP-T58A to upregulate the expression of genes related to fatty acid synthesis and uptake, while downregulating genes associated with fatty acid oxidation. This results in elevated systemic triglyceride levels and renders SHP-T58A mice more susceptible to obesity.⁴⁶ However, in the study by J. Huang *et al.*, leptin and SHP double-mutant mice exhibited increased very low-density lipoprotein (VLDL) secretion and elevated expression of microsomal triglyceride transfer protein, thereby preventing liver steatosis.⁴⁷ It remains unclear whether the primary effect is driven by the leptin mutation or the SHP mutation. Furthermore, endogenous ligands of FXR can promote SHP expression by activating FXR, which in turn inhibits sterol regulatory element-binding protein 1-c (SREBP-1c) expression, thereby correcting hypertriglyceridemia in mice fed a high-fat diet.⁴⁸ Additionally, SHP can bind to liver X receptor α and suppress its expression, regulating multiple genes involved in cholesterol homeostasis.⁴⁹

In the study by L. M. Zhou *et al.*, SHP binds to SREBP1 and inhibits its transcription and translation, leading to downregulation of the de novo lipogenesis gene fatty acid synthase (Fasn) and suppression of de novo lipogenesis.⁵ However, Y. C. Kim *et al.* discovered that SHP inhibits Fasn expression through a different mechanism: SHP recruits DNA methyltransferase-3a to the Fasn promoter, inducing promoter methylation and subsequent epigenetic suppression. Co-expression of DNA methyltransferase-3a and SHP enhances SHP's inhibitory effect on Fasn promoter activity, supporting this mechanism.⁶ Additionally, S. Seok found that SHP can bind to the miR-802 promoter to suppress its transcription, thereby reducing Fasn expression and increasing the expression of the fatty acid β -oxidation gene Macad, ultimately lowering triglyceride levels in the liver.⁷ Studies have also shown that hepatocyte-specific SHP deletion promotes secretion of chemokine (C-C motif) ligand 2 by hepatocytes, leading to macrophage M1 polarization and increased inflammatory responses.⁵⁰ In a study by N. Magee *et al.*, hepatocyte-specific SHP deficiency in mice fed a high-fat cholesterol and fructose diet further increased the expression of inflammatory and fibrotic genes, exacerbating liver inflammation and fibrosis.⁸ Conversely, Lee YK *et al.* found that double knockout of apolipoprotein E and SHP reduced the sensitivity to diet-induced inflammatory responses observed in apolipoprotein E single-knockout mice, without affecting fat accumulation. They suggested that the reduction in inflammatory responses due to SHP knockout is independent of fat accumulation.⁵¹ These seemingly contradictory results may arise from differences in dietary conditions or the fact that SHP is a rapidly degraded protein,⁴² potentially causing inconsistent detection across studies. Significantly, after liver steatosis develops, SHP knockout does not alter the degree of steatosis but increases liver inflammation and fibrosis.⁸ Additionally, SHP can inhibit the transcription of early growth response-1, attenuating bile duct ligation-induced liver fibrosis in mice.⁹ Furthermore, SHP knockout can reduce serum lipopolysaccharide and phenylacetic acid levels by modulating gut microbiota composition, thereby improving MASLD.⁵² Moreover, in the study by S. M. Lee *et al.*, SHP was found to participate in hepatic

lipoprotein metabolism related to circadian rhythms through its interaction with retinoic acid receptor-related orphan receptor (ROR) γ .¹⁰ In conclusion, SHP's regulation of MASLD is multifaceted, and further research is needed to elucidate its overall impact on MASLD. The schematic diagram of the intracellular pathway of the NR0 nuclear orphan receptors is summarized in Figure 1, where red arrows represent activation/promotion, blue arrows represent inhibition, and black arrows indicate regulation.

NR1

REV-ERBs (NR1D1/REV-ERBa, NR1D2/REV-ERB β) and RORs belong to nuclear receptor subfamily 1 and play crucial roles in regulating liver lipid metabolism and circadian rhythms. Studies have found that, compared to wild-type mice, mice with a knockout of the DNA-binding domain (exons 3 and 4) of REV-ERBa exhibit more severe liver steatosis after being fed a high-fat diet,⁵³ suggesting that REV-ERBa has a protective role against liver steatosis. Similarly, J. Guo *et al.* found that overexpression of REV-ERBa inhibited fatty acid synthesis genes and rescued liver steatosis caused by apolipoprotein A5 deficiency.¹¹ Additionally, D. Zhong *et al.* demonstrated that increased REV-ERBa expression reduced cytochrome P450 4A14 and increased acyl-CoA thioesterase 4 levels, leading to reduced liver lipid accumulation and improvements in liver damage, inflammation, and fibrosis.¹² Studies have also shown that increased expression of ROR α promotes macrophage M2 polarization, protecting mice from high-fat diet-induced MASH.⁵⁴ Y. H. Han *et al.* found that ROR α enhances the transcription and translation of Patatin-like phospholipase domain-containing 3 (also known as adiponutrin), which has triacylglycerol (TAG) hydrolase activity, thereby promoting triglyceride (TG) hydrolysis and alleviating liver lipid accumulation.¹³ They also discovered that free fatty acids inhibit ROR α expression via c-Jun N-terminal kinase, reducing Patatin-like phospholipase domain-containing 3 expression and increasing TAG accumulation.¹³ H. J. Kim *et al.* found that ROR α is involved in the transcription of genes related to lysosomal function; hepatocyte-specific ROR α knockout mice exhibited decreased lysosomal acidity and a significant reduction in the number of autolysosomes containing mitochondria and lipid droplets in the liver.¹⁴ Additionally, H. J. Kim *et al.* demonstrated that ROR α knockout downregulated BCL2/adenovirus E1B 19 kDa interacting protein 3 and phosphorylated dynamin-related protein 1, leading to impaired mitochondrial fission in response to nutritional stimuli. This resulted in defects in hepatic mitochondrial quality control, exacerbating diet-induced MASH.¹⁵ Furthermore, perillartine, a compound derived from *Perilla frutescens*, improves lipid deposition and glucose homeostasis in hepatocytes by inhibiting the transcriptional activity of ROR γ , suggesting ROR γ as a potential therapeutic target for MASLD.¹⁶

It is worth mentioning that both REV-ERBa and RORs play important roles in regulating hepatic circadian rhythms.^{17,18,55} A high-fat diet disrupts the circadian rhythms of lipid metabolism, whereas the docosahexaenoic acid metabolite maresin 1 acts as an endogenous ligand for ROR α , enhancing its transcriptional and translational activity.⁵⁴ As a transcription factor, ROR α promotes the transcription of brain and muscle ARNT-like protein 1, whereas REV-ERBa suppresses its transcription by binding to the peroxisome proliferator response element box in the Bmal1 promoter. The balance between ROR α and REV-ERBa participates in regulating circadian genes.¹⁸ This balance also affects insulin-induced gene-2, a key molecule in lipid metabolism,

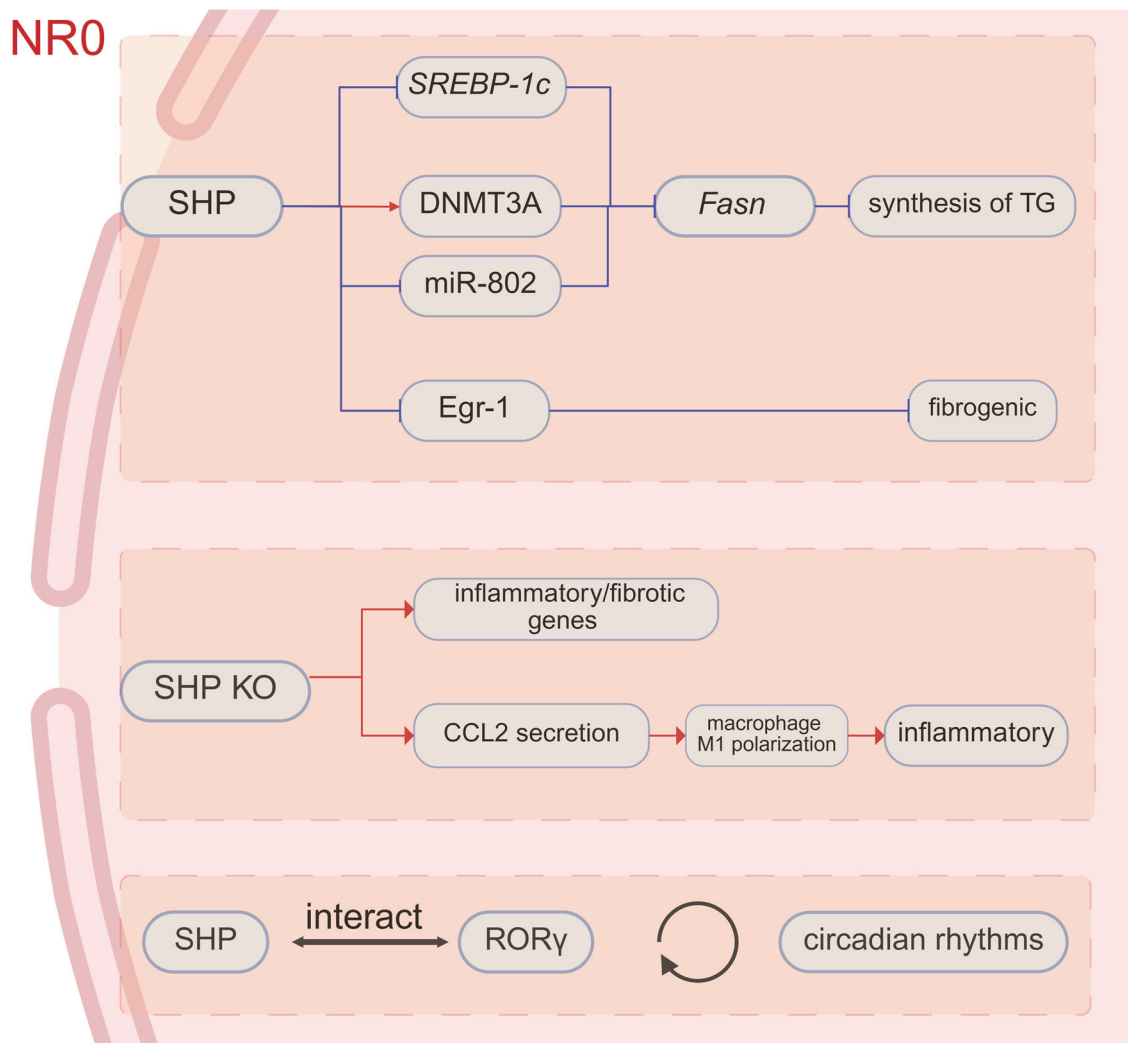


Fig. 1. Intracellular pathways of NR0. Created with BioRender.com. SREBP-1c, sterol regulatory element-binding protein 1c; DNMT3A, DNA methyltransferase 3A; miR-802, microRNA-802; Egr-1, early growth response protein 1; Fasn, fatty acid synthase; TG, triglycerides; KO, knockout; CCL2, C-C motif chemokine ligand 2; M1, classically activated macrophages; ROR γ , retinoid-related orphan receptor gamma.

thereby regulating downstream SREBP activation and lipid accumulation.¹⁸ In the study by D. Li *et al.*, compared to HFD mice, high-sucrose diet mice exhibited increased circadian amplitude and median levels of ROR γ , suggesting that ROR γ may regulate the circadian rhythm system under high-sucrose diet conditions. Further research revealed that ROR γ deficiency suppresses *SREBP-1c* gene expression and reduces hepatic lipid levels.¹⁹ The schematic diagram of the intracellular pathway of the NR1 nuclear orphan receptors is summarized in Figure 2.

NR2

In current MASLD research, significant progress has been made in studying the nuclear orphan receptor NR2 family member NR2A1 (hepatocyte nuclear factor 4 alpha, HNF4 α). HNF4 α is indispensable for hepatocyte differentiation and is highly expressed in hepatocytes. It regulates genes involved in liver-specific functions such as nutrient metabolism, drug metabolism, urea clearance, bile acid synthesis, and coagulation factor production, all of which are crucial for main-

taining liver health.⁵⁶ HNF4 α activity decreases significantly as the liver progresses from dysplasia to early cirrhosis and from cirrhosis to early hepatocellular carcinoma, marking a critical point of liver function decline.⁵⁶

Studies have shown that liver-specific deletion of Ssu72 phosphatase downregulates HNF4 α transcription and translation, leading to hepatocyte dedifferentiation and contributing to the progression of steatohepatitis-associated hepatocellular carcinoma.⁵⁷ N-trans caffeoyltyramine and N-trans feruloyltyramine can activate HNF4 α , increasing the expression of downstream genes such as Spinster homolog 2 and CYP26A1. This enhances dihydroceramide production and action, promoting lipid autophagy and alleviating lipid accumulation.⁵⁸ Further studies have revealed that N-trans caffeoyltyramine increases mitochondrial mass by enhancing the activity of the PPARGC1A pathway, thereby promoting fatty acid oxidation, reducing mitochondrial stress, and slowing MASLD progression.²⁰ D. H. Lee and colleagues found that the expression of autophagy-related genes is suppressed in fatty liver, while HNF4 α can directly bind to the promoter region of UNC-51-like kinase 1, increasing its transcription

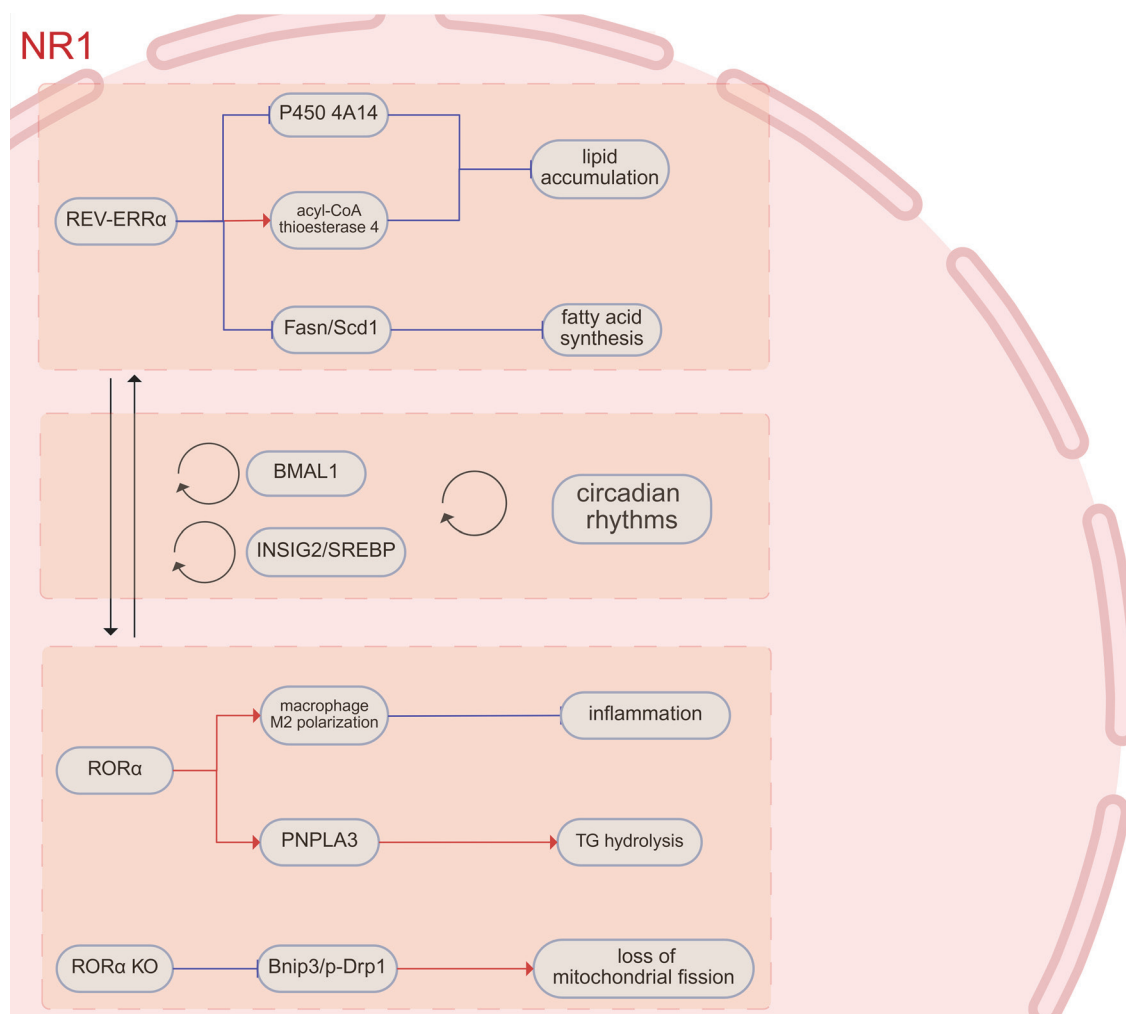


Fig. 2. Intracellular pathways of NR1. Created with BioRender.com. REV-ERR α , reverse strand of ERB-alpha; P450 4A14, cytochrome P450 family 4 subfamily A member 14; Fasn, fatty acid synthase; Scd1, stearoyl-CoA desaturase 1; BMAL1, brain and muscle ARNT-like 1; INSIG2, insulin induced gene 2; SREBP, sterol regulatory element-binding protein; ROR α , retinoid-related orphan receptor alpha; M2, alternatively activated macrophages; PNPLA3, patatin-like phospholipase domain-containing protein 3; TG, triglycerides; KO, knockout; Bnip3, BCL2 interacting protein 3; p-Drp1, phosphorylated dynamin-related protein 1.

in hepatocytes and improving autophagy activity.²¹ HNF4 α is also a key regulator of triglyceride hydrolysis and fatty acid oxidation. Liver-specific overexpression of HNF4 α can prevent MASH induced by a high-fat/cholesterol/fructose diet by inhibiting p53.⁵⁹ Studies have shown that HNF4 α increases the promoter activity of the murine carboxylesterase 2 gene by binding to DR-1 elements (direct repeats separated by one nucleotide) in the proximal promoter. This regulation modulates lipolysis, endoplasmic reticulum stress, and lipogenesis, thereby preventing hepatic steatosis.⁶⁰ Thus, the reduction of carboxylesterase 2 in MASH patients is likely due to decreased HNF4 α expression. The phosphatidylinositol 3-kinase signaling pathway also plays a crucial role in lipid metabolism. PIK3R3, the 62 kDa regulatory subunit of phosphatidylinositol 3-kinase, promotes hepatic fatty acid oxidation by inducing PPAR α expression, thereby ameliorating hepatic steatosis in HFD-induced mice. However, this pathway requires HNF4 α involvement. The deletion of HNF4 α suppresses the PIK3R3-PPAR α pathway, inhibiting fatty acid β -oxidation.⁶¹ Notably, C. I. Kasano-Camones found that in HNF4 α liver-specific knockout mice fed a Western diet, despite decreased PPAR α mRNA and protein levels, increased

PPAR γ coactivator 1 α expression promoted PPAR α transactivation, activating downstream target genes that led to steatosis and advanced MASLD progression.⁶² Additionally, J. Ahn *et al.* discovered that HNF4 α is recruited to the upstream region of the miR-467b-3p transcription start site, mediating its upregulation. miR-467b-3p directly binds to the 3' untranslated region of glycerol-3-phosphate acyltransferase-1, suppressing its expression, thereby reducing TG synthesis and alleviating steatosis.²² HNF4 α is also involved in lipid transport; liver-specific knockout of HNF4 α alters the structure and composition of HDL, reducing its antioxidant capacity and affecting genes involved in HDL maturation and modification. This leads to decreased levels of HDL-C, LDL-C, phospholipids, and TG in mice.²³ It is generally accepted that a high-fat diet reduces HNF4 α expression in hepatocytes.^{60,63} However, D. Yu and colleagues proposed that the effects of an HFD are not mediated by altering HNF4 α expression but rather by increasing oxidative stress, which induces protein kinase C phosphorylation at Ser78. This phosphorylation inhibits HNF4 α nuclear translocation, ultimately blocking apolipoprotein B transcription, reducing hepatic VLDL secretion, and promoting hepatic TAG accumulation.^{64,65} Therefore, the

oxidative stress/protein kinase C/HNF4 α /ApoB pathway may serve as a novel therapeutic target for HFD-induced fatty liver disease. Beyond lipid metabolism, HNF4 α also plays a crucial role in bile acid metabolism. In a study by Y. J. Roh *et al.*, HNF4 α knockdown suppressed the expression of genes related to bile acid uptake and synthesis, reducing bile acid toxicity and alleviating steatohepatitis and liver fibrosis. However, while HNF4 α knockdown decreases bile acid toxicity, it also inhibits the expression of genes involved in fatty acid oxidation (CPT1A and ACOX1) and fat export (ApoB and MTTP), leading to increased lipotoxicity.²⁴ Thus, HNF4 α appears to have opposing roles in lipid and bile acid metabolism.

Other orphan nuclear receptors in the NR2 family also influence MASLD progression. Q. Xiong *et al.* found that in mice with high-fat diet-induced liver steatosis, expression of nuclear receptor subfamily 2 group E member 1 (NR2E1, TLX) was decreased. Compared to wild-type mice, NR2E1 knockout mice showed increased expression of cholesterol synthesis-related genes (HMGCR, SREBP-1), fatty acid synthesis genes (FAS, ACC), and suppressed expression of genes related to lipid β -oxidation (CPT1A, PPAR α). This led to increased cholesterol and fatty acid synthesis and aggravated liver steatosis.²⁵ In contrast, high-fat diets increase the expression of NR2F2. NR2F2 knockout results in elevated adiponectin levels, which alleviate fat accumulation and steatosis in the liver. Additionally, NR2F2 knockout suppresses the expression of α -smooth muscle actin and Pnpla3, inhibiting the activation of hepatic stellate cells.²⁶ It is worth noting that liver-specific overexpression of NR2F6 can increase hepatic triglyceride accumulation without affecting body weight or food intake. Further studies have shown that NR2F6 promotes liver triglyceride accumulation by binding to the CD36 promoter, increasing CD36 expression, and enhancing hepatic fatty acid uptake. This effect is not mediated by changes in circulating β -hydroxybutyrate levels or VLDL secretion rate, ultimately leading to steatosis.²⁷ The schematic diagram of the intracellular pathway of NR2 nuclear orphan receptors is summarized in Figure 3.

NR3

ERRs α , β , and γ , members of nuclear receptor subfamily 3, are expressed in various tissues and play important roles in regulating bone homeostasis, energy metabolism, and cancer progression.⁶⁶ Studies have shown that environmental pollutants triclocarban and triclosan can bind to ERR α and ERR γ , enhancing their transcriptional activity. This upregulates genes related to lipogenesis, thereby exacerbating hepatic lipid accumulation induced by a high-fat diet.²⁸ In human MAFL/MASH cohorts, particularly at MASH stages F0–F2, ERR α expression positively correlates with MASH-related genes,⁶⁷ suggesting that ERR α contributes to MASH progression. In mice fed a high-fat diet, ERR α expression is upregulated. However, treatment with the ERR α inhibitor ERR-PA suppresses the expression of two key enzymes involved in de novo lipogenesis, Fasn and acetyl-CoA carboxylase, indicating that ERR α promotes MASLD progression by influencing de novo lipogenesis.²⁹ ERR α knockout mice exhibit resistance to HFD-induced MASLD, showing reduced white adipose tissue storage and impaired hepatic lipid accumulation. However, under fasting and refeeding conditions, ERR α knockout impairs the reversal of fasting-induced MASLD, indicating that ERR α deletion plays a preventive role in MASLD development rather than a therapeutic one.⁶⁸ Moreover, ERR α can promote insulin resistance by downregulating oxidative phosphorylation genes, with insulin resistance being a key mechanism in MASLD pathogenesis.³⁰ Interestingly, during the progres-

sion from steatosis to steatohepatitis in mice, the mRNA and protein levels of ERR α and Ribosomal large subunit protein 1 are downregulated, leading to reduced translation of autophagy-related proteins and inhibited autophagic activity.³¹ This suggests ERR α plays distinct roles at different MASLD stages via diverse mechanisms. Furthermore, intermittent fasting was found to promote the expression of ERR α and Ribosomal large subunit protein 1, providing valuable insight for rational dietary interventions in MASH.³¹ Comparative studies revealed that, in fasting conditions, female mice express higher levels of ERR α than male mice, which leads to sex differences in VLDL-TG assembly and secretion. Liver-specific ERR α deficiency in female mice increased hepatic fat accumulation and worsened MASLD progression, potentially explaining gender differences in MASLD pathogenesis.³² Additionally, ovariectomized mice showed downregulated expression of ERR α , ApoB, and MTTP, developing fatty liver. Overexpression of ERR α reversed these effects, suggesting that estrogen's protective effect against MASLD is mediated through ERR α .³² The schematic diagram of the intracellular pathway of the NR3 nuclear orphan receptor family is summarized in Figure 4.

NR4

The NR4A subfamily of nuclear receptors (NR4A1/Nur77/TR3/NGFI-B, NR4A2/Nurr1, NR4A3/Nor1) are important regulatory proteins involved in various disease states and metabolic conditions, particularly in the liver and muscle.^{69,70} NR4A expression is upregulated in the adipose tissue of patients with severe obesity, and following weight loss surgery, NR4A levels return to those observed in normal lean controls.⁷⁰ Bioinformatics analyses indicate that NR4A1 is downregulated in the livers of MASLD patients, where it is implicated in NOD-like receptor and JAK-STAT signaling pathways. NR4A1 plays a role in regulating mitochondrial autophagy and immune activation during MASLD progression, with its expression significantly negatively correlated with infiltration of pro-inflammatory M1 macrophages. Additionally, NR4A2 is dysregulated in MAFLD and may modulate immune responses in the disease, serving as a potential diagnostic marker for MASLD.^{71–75}

J. He *et al.* demonstrated NR4A1's role in macrophages, showing that hyperoside upregulates NR4A1 expression, promoting the conversion of pro-inflammatory M1 macrophages to anti-inflammatory M2 macrophages, thereby alleviating MASLD in HFD-fed mice.³³ However, H. Zhou *et al.* reported that NR4A1 can phosphorylate the DNA-dependent protein kinase catalytic subunit. Phosphorylated DNA-dependent protein kinase catalytic subunit dissociates from Ku80 and phosphorylates p53, which increases the expression of dynamin-related protein 1, leading to mitochondrial fission. This mitochondrial dysfunction disrupts mitochondrial homeostasis in MASLD, potentially causing hepatocyte injury or death.³⁴ This finding partially explains the conclusion from Y. Xu *et al.* that "the inhibitory effect of HNF4 α on MASLD is partly mediated through the p53 pathway, as overexpression of p53 can partially counteract the inhibitory effect of HNF4 α on steatohepatitis".⁵⁹ In addition, NR4A1 can attenuate homocysteine-induced steatosis both in vivo and in vitro, suggesting its potential as a therapeutic target for homocysteine-related MASLD.⁷⁶ Studies have found that overexpression of NR4A2 upregulates genes related to lipogenesis, liver inflammation, and steatosis, exacerbating steatosis, liver inflammation, and fibrosis.³⁵ Notably, upon stimulation of hepatic stellate cells with the strong inducer PDGF-BB, NR4A2 expression

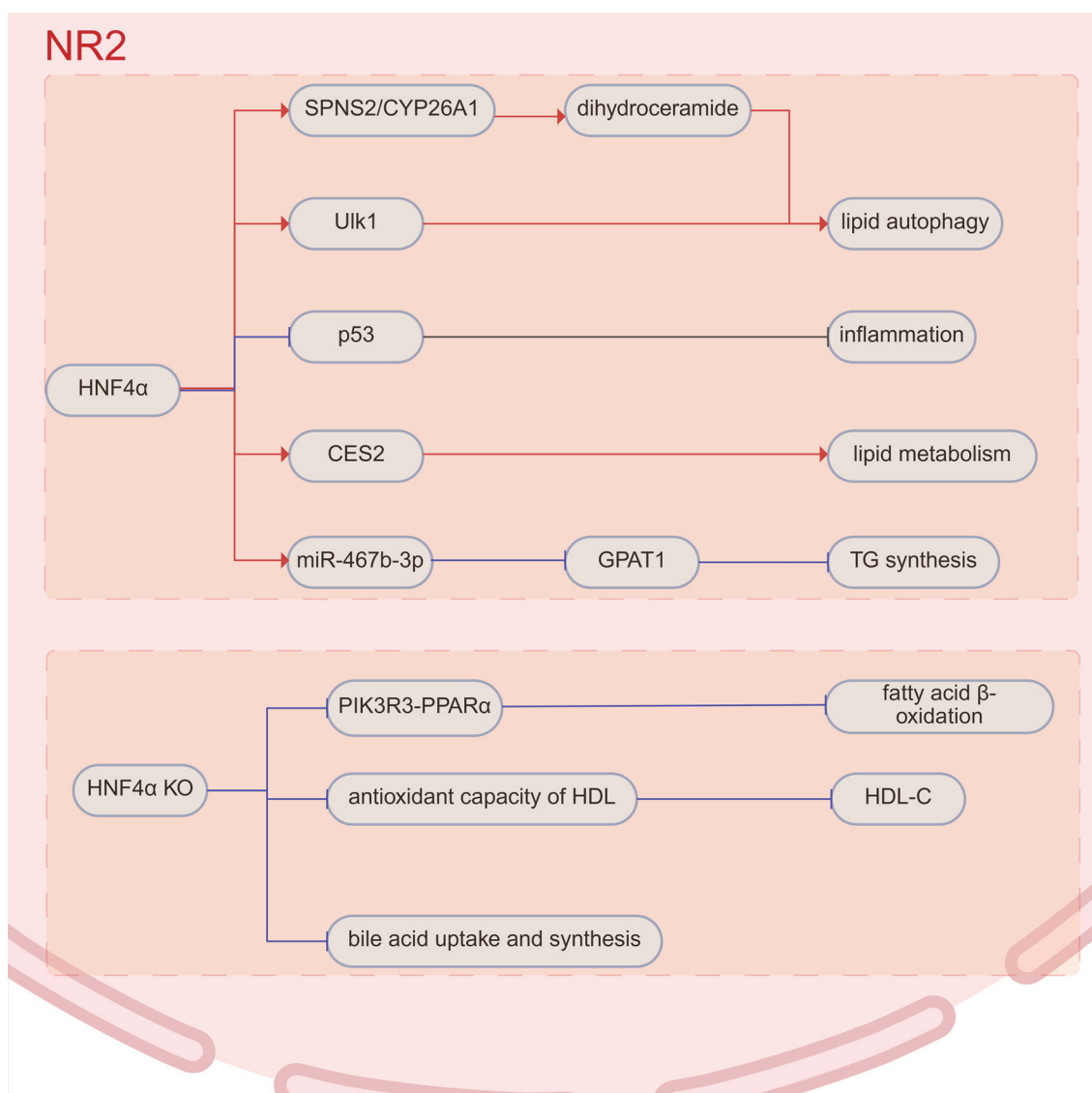


Fig. 3. Intracellular pathways of NR2. Created with BioRender.com. SPNS2, spinster homolog 2; CYP26A1, cytochrome P450 family 26 subfamily A member 1; Ulk1, unc-51 like autophagy activating kinase 1; CES2, carboxylesterase 2; miR-467b-3p, microRNA-467b-3p; GPAT1, glycerol-3-phosphate acyltransferase 1; TG, triglycerides; PIK3R3, phosphoinositide-3-kinase regulatory subunit 3; PPARα, peroxisome proliferator activated receptor alpha; β-oxidation, beta-oxidation; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; HNF4α, hepatocyte nuclear factor 4-alpha.

decreases alongside downregulation of phosphorylation levels of ERK1/2, P38, and c-Jun N-terminal kinase—key components of the MAPK pathway involved in liver fibrosis. Concurrently, the fibrosis marker α-smooth muscle actin significantly increases, suggesting that NR4A2 contributes to extracellular matrix accumulation in liver fibrosis through regulation of the MAPK pathway.³⁶ The schematic diagram of the intracellular pathway of NR4 nuclear orphan receptors is summarized in Figure 4.

NR5

NR5A2 (liver receptor homolog-1 (LRH-1)), a member of the NR5A subfamily of nuclear receptors, is expressed in endo-derm-derived tissues, including the intestine, liver, exocrine pancreas, and ovaries. It plays a critical role in development, reverse cholesterol transport, bile acid homeostasis,

and steroidogenesis.^{77,78} N. Sahini and J. Borlak performed liver biopsies on healthy controls and MASLD patients and found that various transcription factors, including LRH-1, were suppressed in the livers of MASLD patients.⁷⁹ Studies in diet-induced MASH mice have shown that phosphatidylcholine levels in the liver are decreased, and supplementation with phosphatidylcholine reduces MASH progression by mechanisms involving activation of B cell signaling via the LRH-1/PPARγ2/nuclear factor κ-light-chain enhancer pathway.⁸⁰ LRH-1 plays a crucial role in hepatic lipid storage and phospholipid composition. Research has demonstrated that deletion of LRH-1 inhibits two key enzymes in arachidonic acid biosynthesis—long-chain fatty acid desaturase and elongase—resulting in decreased arachidonic acid-containing phospholipids. This disrupts liver phospholipid composition, leading to abnormal lipid accumulation and non-dietary-related hepatic steatosis.³⁷ Notably, dilauroyl phosphatidylcho-

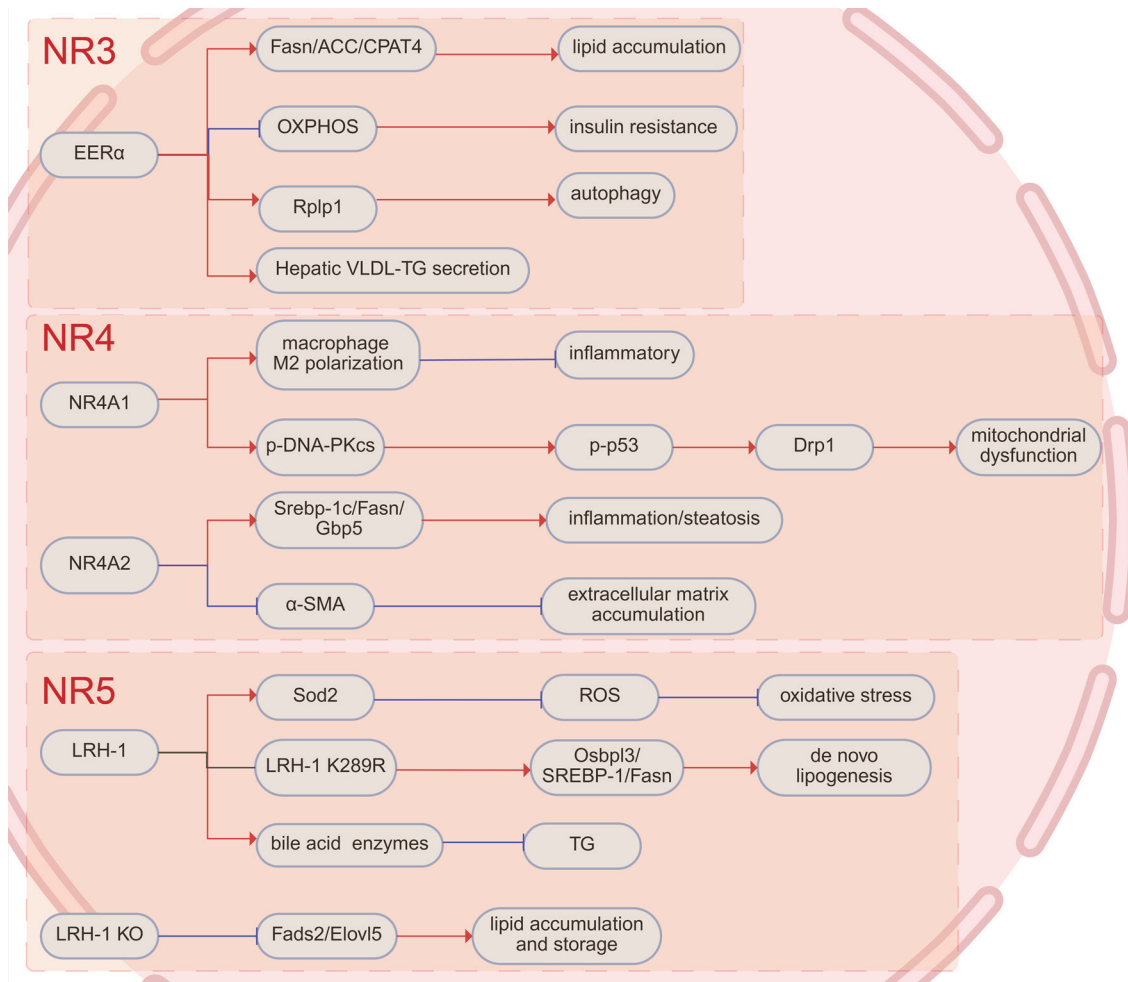


Fig. 4. Intracellular pathways of NR3-5. Created with BioRender.com. ERRα, estrogen-related receptor alpha; ACC, acetyl-CoA carboxylase; GPAT4, glycerol-3-phosphate acyltransferase 4; OXPHOS, oxidative phosphorylation; Rplp1, ribosomal protein lateral stalk subunit P1; VLDL, very low-density lipoprotein; TG, triglycerides; NR4A1, nuclear receptor subfamily 4 group A member 1; NR4A2, nuclear receptor subfamily 4 group A member 2; M2, alternatively activated macrophages; p-DNA-PKcs, phosphorylated DNA-dependent protein kinase catalytic subunit; P-p53, phosphorylated tumor protein p53; Drp1, dynamin-related protein 1; SREBP-1α, sterol regulatory element-binding protein 1-alpha; Gbp5, guanylate binding protein 5; α-SMA, alpha smooth muscle actin; LRH-1, liver receptor homolog-1; K289R, lysine-289 to arginine mutation; Sod2, superoxide dismutase 2; ROS, reactive oxygen species; Osbpl3, oxysterol binding protein-like 3; KO, knockout; Fads2, fatty acid desaturase 2; Elovl5, ELOVL fatty acid elongase 5.

line (DLPC), an unusual phosphatidylcholine species with two saturated 12-carbon fatty acid acyl chains, acts as an *in vitro* agonist of LRH-1. DLPC induces bile acid biosynthetic enzymes in the liver, increases bile acid levels, reduces liver triglycerides and serum glucose, and alleviates hepatic steatosis. Furthermore, DLPC improves glucose homeostasis in two mouse models of insulin resistance, indicating that LRH-1 regulates bile acid metabolism and glucose homeostasis via the phosphatidylcholine pathway.⁸¹ Additionally, LRH-1 directly regulates the expression of Fasn and promotes the transcription factor ChREBP, which directly or indirectly controls all components of *de novo* lipogenesis.⁷⁸ It is important to note that small ubiquitin-related modifier modification-deficient LRH-1—specifically the LRH-1 K289R mutant mouse—is more susceptible to MASLD when fed a high-fat diet. This mutation promotes Osbpl3 expression and subsequently induces SREBP-1 signaling at the transcriptional level, leading to increased Fasn expression and enhanced *de novo* lipogenesis.³⁸ Additionally, LRH-1 binds to the promoter of superoxide dismutase 2, promoting its expression and re-

ducing reactive oxygen species production induced by high palmitate concentrations, thereby alleviating oxidative stress in MASLD.⁸² It is noteworthy that SHP can transcriptionally repress LRH-1 by recruiting class III histone deacetylase SIRT1, which inhibits LRH-1 target gene promoter activity and mRNA levels.³⁹ Conversely, LRH-1 can activate the SHP promoter, promoting SHP expression.⁸³ This bidirectional interaction affects their respective roles in MASLD. The SHP-T58A mutant disrupts its interaction with LRH-1, resulting in derepression of SHP/LRH-1 target genes related to bile acid and lipid synthesis, thereby promoting MASLD progression.⁴⁶ The schematic diagram of the intracellular pathway of the NR5 nuclear orphan receptor family is summarized in Figure 4.

Targeting nuclear orphan receptors for the treatment of MAFLD

Given the critical role of nuclear orphan receptors in lipid metabolism, inflammation, and fibrosis processes in MA-

SLD, researchers have begun exploring their therapeutic potential. Several natural compounds have been identified that improve MASLD by modulating nuclear orphan receptors. For instance, hyperoside acts on SHP,⁸⁴ 6-gingerol targets HNF4 α ,²² and Angelica sinensis polysaccharide regulates ERR α .⁸⁵ Additionally, *Inonotus obliquus* and its bioactive compound inotodiol exert anti-MASLD effects by modulating the FXR/SHP/SREBP-1c pathway.⁸⁶ In high-fat diet-fed mouse models, long-term oral administration of HNF4 α agonists (e.g., NCT) enhances mitochondrial quality and function, preventing weight gain and hepatic steatosis.²⁰ The selective ERR α agonist JND003 enhances the transactivation of ERR α downstream target genes while improving insulin sensitivity and alleviating fatty liver symptoms.⁸⁷ Dapagliflozin, a selective sodium-glucose cotransporter-2 inhibitor widely used to treat type 2 diabetes,⁸⁸ reduces de novo lipogenesis in the livers of db/db mice by upregulating FXR/SHP and downregulating liver X receptor α /SREBP-1c.⁸⁹ To date, no pharmacological agents targeting nuclear orphan receptors have been approved for MASLD therapy, highlighting a significant unmet clinical need. Given their regulatory role in the interconnected pathways of lipid metabolism, inflammation, and fibrosis, the development of novel drugs targeting these receptors represents a promising therapeutic strategy.

Conclusions

In summary, orphan nuclear receptors influence the onset and progression of MASLD, particularly in lipid metabolism, inflammation, autophagy, and cholesterol metabolism. These receptors may play either similar or opposing roles within the same pathological and physiological processes, forming an intricate network of interactions. Among them, SHP and HNF4 α have been studied extensively. SHP participates in MASLD progression by influencing lipid synthesis, liver inflammation, fibrosis, and circadian rhythms, while also interacting with other orphan nuclear receptors such as ROR γ and LXR-1. HNF4 α , in contrast, influences MASLD progression primarily through its impact on lipid and bile acid metabolism. Although orphan nuclear receptors play important roles in MASLD, few drugs currently target these receptors for MASLD treatment. Therefore, the development of therapeutics aimed at orphan nuclear receptors is essential. Moreover, the fact that some orphan nuclear receptors exert opposing effects in the same physiological processes is both intriguing and worthy of further investigation. Additional research is necessary to elucidate these underlying mechanisms, thereby providing a theoretical foundation for the potential clinical use of orphan nuclear receptors as therapeutic targets in the future. In this review, we discuss the contributions of distinct nuclear orphan receptors to MASLD pathogenesis, evaluate emerging therapeutic strategies targeting these receptors, and highlight promising avenues for future MASLD intervention.

Funding

This work was supported by the National Key Research and Development Program of China (2023YFC2507405), and the Interdisciplinary Innovative Talents Foundation from Renmin Hospital of Wuhan University (JCRCFZ-2022-017).

Conflict of interest

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

Author contributions

Study concept and design (HL), drafting of the manuscript (JC), critical revision of the manuscript for important intellectual content (ZH), administrative, technical, material support, and study supervision (MC). All authors have approved the final version and publication of the manuscript.

References

- Quek J, Chan KE, Wong ZY, Tan C, Tan B, Lim WH, *et al*. Global prevalence of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in the overweight and obese population: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2023;8(1):20–30. doi:10.1016/s2468-1253(22)00317-x, PMID:36400097.
- Huang DQ, Wong VWS, Rinella ME, Boursier J, Lazarus JV, Yki-Järvinen H, *et al*. Metabolic dysfunction-associated steatotic liver disease in adults. *Nat Rev Dis Primers* 2025;11(1):14. doi:10.1038/s41572-025-00599-1, PMID:40050362.
- Targher G, Byrne CD, Tilg H. MASLD: a systemic metabolic disorder with cardiovascular and malignant complications. *Gut* 2024;73(4):691–702. doi:10.1136/gutjnl-2023-330595, PMID:38228377.
- Guzmán A, Hughes CHK, Murphy BD. Orphan nuclear receptors in angiogenesis and follicular development. *Reproduction* 2021;162(3):R35–r54. doi:10.1530/rep-21-0118, PMID:34270446.
- Zhou LM, Fan JH, Xu MM, Xiong MY, Wang QJ, Chai X, *et al*. Epiberberine regulates lipid synthesis through SHP (NR0B2) to improve non-alcoholic steatohepatitis. *Biochim Biophys Acta Mol Basis Dis* 2023;1869(4):166639. doi:10.1016/j.bbdis.2023.166639, PMID:36638873.
- Kim YC, Seok S, Zhang Y, Ma J, Kong B, Guo G, *et al*. Intestinal FGF15/19 physiologically repress hepatic lipogenesis in the late fed-state by activating SHP and DNMT3A. *Nat Commun* 2020;11(1):5969. doi:10.1038/s41467-020-19803-9, PMID:33235221.
- Seok S, Sun H, Kim YC, Kemper B, Kemper JK. Defective FXR-SHP Regulation in Obesity Aberrantly Increases miR-802 Expression, Promoting Insulin Resistance and Fatty Liver. *Diabetes* 2021;70(3):733–744. doi:10.2337/db20-0856, PMID:33328206.
- Magee N, Zou A, Ghosh P, Ahamed F, Delker D, Zhang Y. Disruption of hepatic small heterodimer partner induces dissociation of steatosis and inflammation in experimental nonalcoholic steatohepatitis. *J Biol Chem* 2020;295(4):994–1008. doi:10.1074/jbc.RA119.010233, PMID:31831621.
- Zhang Y, Xu N, Xu J, Kong B, Copple B, Guo GL, *et al*. E2F1 is a novel fibrogenic gene that regulates cholestatic liver fibrosis through the Egr-1/SHP/EID1 network. *Hepatology* 2014;60(3):919–930. doi:10.1002/hep.27121, PMID:24619556.
- Lee SM, Zhang Y, Tsuchiya H, Smalling R, Jetten AM, Wang L. Small heterodimer partner/neuronal PAS domain protein 2 axis regulates the oscillation of liver lipid metabolism. *Hepatology* 2015;61(2):497–505. doi:10.1002/hep.27437, PMID:25212631.
- Guo J, Miao G, Zhang W, Shi H, Lai P, Xu Y, *et al*. Depletion of ApoA5 aggravates spontaneous and diet-induced nonalcoholic fatty liver disease by reducing hepatic NR1D1 in hamsters. *Theranostics* 2024;14(5):2036–2057. doi:10.7150/thno.91084, PMID:38505614.
- Zhong D, Cai J, Hu C, Chen J, Zhang R, Fan C, *et al*. Inhibition of mPG-ES-2 ameliorates NASH by activating NR1D1 via heme. *Hepatology* 2023;78(2):547–561. doi:10.1002/hep.32671, PMID:35839302.
- Han YH, Kim HJ, Lee MO. ROR α regulates hepatic lipolysis by inducing transcriptional expression of PNPLA3 in mice. *Mol Cell Endocrinol* 2021;522:111122. doi:10.1016/j.mce.2020.111122, PMID:33347955.
- Kim HJ, Han YH, Kim JY, Lee MO. ROR α Enhances Lysosomal Acidification and Autophagic Flux in the Hepatocytes. *Hepatol Commun* 2021;5(12):2121–2138. doi:10.1002/hep4.1785, PMID:34558854.
- Kim HJ, Han YH, Na H, Kim JY, Kim T, Kim HJ, *et al*. Liver-specific deletion of ROR α aggravates diet-induced nonalcoholic steatohepatitis by inducing mitochondrial dysfunction. *Sci Rep* 2017;7(1):16041. doi:10.1038/s41598-017-16077-y, PMID:29167529.
- Xiao Y, Xiao L, Li M, Liu S, Wang Y, Huang L, *et al*. Perillartine protects against metabolic associated fatty liver in high-fat diet-induced obese mice. *Food Funct* 2023;14(2):961–977. doi:10.1039/d2fo02227c, PMID:36541423.
- Zhao H, Han G, Jiang Z, Gao D, Zhang H, Yang L, *et al*. Identification of BMAL1-Regulated circadian genes in mouse liver and their potential association with hepatocellular carcinoma: Gys2 and Upp2 as promising candidates. *Biochem Biophys Res Commun* 2024;696:149422. doi:10.1016/j.bbrc.2023.149422, PMID:38183795.
- Chen R, Zuo Z, Li Q, Wang H, Li N, Zhang H, *et al*. DHA substitution overcomes high-fat diet-induced disturbance in the circadian rhythm of lipid metabolism. *Food Funct* 2020;11(4):3621–3631. doi:10.1039/c9fo02606a, PMID:32292967.
- Li D, Ikaga R, Ogawa H, Yamazaki T. Different expressions of clock genes in fatty liver induced by high-sucrose and high-fat diets. *Chronobiol Int* 2021;38(5):762–778. doi:10.1080/07420528.2021.1889579, PMID:33612041.
- Veeriah V, Lee SH, Levine F. Long-term oral administration of an HNF4 α agonist prevents weight gain and hepatic steatosis by promoting increased mitochondrial mass and function. *Cell Death Dis* 2022;13(1):89. doi:10.1038/s41419-022-04521-5, PMID:35087037.

- [21] Lee DH, Park SH, Ahn J, Hong SP, Lee E, Jang YJ, *et al*. Mir214-3p and Hnf4a/Hnf4a reciprocally regulate Ulk1 expression and autophagy in non-alcoholic hepatic steatosis. *Autophagy* 2021;17(9):2415–2431. doi:10.1080/15548627.2020.1827779, PMID:33078654.
- [22] Ahn J, Lee H, Jung CH, Ha SY, Seo HD, Kim YI, *et al*. 6-Gingerol Ameliorates Hepatic Steatosis via HNF4a/miR-467b-3p/GPAT1 Cascade. *Cell Mol Gastroenterol Hepatol* 2021;12(4):1201–1213. doi:10.1016/j.jcmgh.2021.06.007, PMID:34139323.
- [23] Thymiakou E, Othman A, Hornemann T, Kardassis D. Defects in High Density Lipoprotein metabolism and hepatic steatosis in mice with liver-specific ablation of Hepatocyte Nuclear Factor 4A. *Metabolism* 2020;110:154307. doi:10.1016/j.metabol.2020.154307, PMID:32622843.
- [24] Roh YJ, Kim Y, Lee JS, Oh JH, Lee SM, Yoon EL, *et al*. Regulation of Hepatocyte Nuclear Factor 4a Attenuated Lipotoxicity but Increased Bile Acid Toxicity in Non-Alcoholic Fatty Liver Disease. *Life (Basel)* 2022;12(11):1682. doi:10.3390/life12111682, PMID:36362837.
- [25] Xiong Q, Wu Y, Yang M, Wu G, Wang Y, Wang H, *et al*. Nr2e1 ablation impairs liver glucolipid metabolism and induces inflammation, high-fat diets amplify the damage. *Biomed Pharmacother* 2019;120:109503. doi:10.1016/j.biopha.2019.109503, PMID:31590127.
- [26] Mao Z, Zhao J, Cui F, Li Z, Cao J, Zhou J, *et al*. STUB1 increases adiponectin expression by inducing ubiquitination and degradation of NR2F2, thereby reducing hepatic stellate cell activation and alleviating non-alcoholic fatty liver disease. *Tissue Cell* 2024;88:102345. doi:10.1016/j.tice.2024.102345, PMID:38471267.
- [27] Zhou B, Jia L, Zhang Z, Xiang L, Yuan Y, Zheng P, *et al*. The Nuclear Orphan Receptor NR2F6 Promotes Hepatic Steatosis through Upregulation of Fatty Acid Transporter CD36. *Adv Sci (Weinh)* 2020;7(21):2002273. doi:10.1002/advs.202002273, PMID:33173745.
- [28] Li X, Zhang JD, Xiao H, He S, He TT, Ren XM, *et al*. Triclocarban and triclosan exacerbate high-fat diet-induced hepatic lipid accumulation at environmental related levels: The potential roles of estrogen-related receptors pathways. *Sci Total Environ* 2023;858(Pt 3):160079. doi:10.1016/j.scitotenv.2022.160079, PMID:36372182.
- [29] Chen CY, Li Y, Zeng N, He L, Zhang X, Tu T, *et al*. Inhibition of Estrogen-Related Receptor α Blocks Liver Steatosis and Steatohepatitis and Attenuates Triglyceride Biosynthesis. *Am J Pathol* 2021;191(7):1240–1254. doi:10.1016/j.ajpath.2021.04.007, PMID:33894178.
- [30] Xia H, Dufour CR, Giguère V. ERR α as a Bridge Between Transcription and Function: Role in Liver Metabolism and Disease. *Front Endocrinol (Lausanne)* 2019;10:206. doi:10.3389/fendo.2019.00206, PMID:31024446.
- [31] Tripathi M, Gauthier K, Sandireddy R, Zhou J, Gupta P, Sakthivel S, *et al*. Esrra regulates Rplp1-mediated translation of lysosome proteins suppressed in metabolic dysfunction-associated steatohepatitis and reversed by alternate day fasting. *Mol Metab* 2024;87:101997. doi:10.1016/j.molmet.2024.101997, PMID:39032642.
- [32] Yang M, Liu Q, Huang T, Tan W, Qu L, Chen T, *et al*. Dysfunction of estrogen-related receptor alpha-dependent hepatic VLDL secretion contributes to sex disparity in NAFLD/NASH development. *Theranostics* 2020;10(24):10874–10891. doi:10.7150/thno.47037, PMID:33042259.
- [33] Sun B, Zhang R, Liang Z, Fan A, Kang D. Hyperoside attenuates non-alcoholic fatty liver disease through targeting Nr4A1 in macrophages. *Int Immunopharmacol* 2021;94:107438. doi:10.1016/j.intimp.2021.107438, PMID:33611063.
- [34] Zhou H, Zhu P, Wang J, Toan S, Ren J. DNA-PKcs promotes alcohol-related liver disease by activating Drp1-related mitochondrial fission and repressing FUNDC1-required mitophagy. *Signal Transduct Target Ther* 2019;4:56. doi:10.1038/s41392-019-0094-1, PMID:31839999.
- [35] Li B, Yang Z, Mao F, Gong W, Su Q, Yang J, *et al*. Downregulation of microRNA-145a-5p promotes steatosis-to-NASH progression through up-regulation of Nr4a2. *J Hepatol* 2023;79(5):1096–1109. doi:10.1016/j.jhep.2023.06.019, PMID:37463623.
- [36] Chen P, Li J, Huo Y, Lu J, Wan L, Li B, *et al*. Orphan nuclear receptor NR4A2 inhibits hepatic stellate cell proliferation through MAPK pathway in liver fibrosis. *PeerJ* 2015;3:e1518. doi:10.7717/peerj.1518, PMID:26713258.
- [37] Miranda DA, Krause WC, Cazenave-Gassiot A, Suzawa M, Escusa H, Foo JC, *et al*. LRH-1 regulates hepatic lipid homeostasis and maintains arachidonic acid phospholipid pools critical for phospholipid diversity. *JCI Insight* 2018;3(5):e96151. doi:10.1172/jci.insight.96151, PMID:29515023.
- [38] Stein S, Lemos V, Xu P, Demagny H, Wang X, Ryu D, *et al*. Impaired SUMOylation of nuclear receptor LRH-1 promotes nonalcoholic fatty liver disease. *J Clin Invest* 2017;127(2):583–592. doi:10.1172/jci85499, PMID:28094767.
- [39] Chanda D, Xie YB, Choi HS. Transcriptional corepressor SHP recruits SIRT1 histone deacetylase to inhibit LRH-1 transactivation. *Nucleic Acids Res* 2010;38(14):4607–4619. doi:10.1093/nar/gkq227, PMID:20375098.
- [40] Li L, Galichon P, Xiao X, Figueroa-Ramirez AC, Tamayo D, Lee JJ, *et al*. Orphan nuclear receptor COUP-TFII enhances myofibroblast glycolysis leading to kidney fibrosis. *EMBO Rep* 2021;22(6):e51169. doi:10.15252/embr.202051169, PMID:34031962.
- [41] Misra J, Kim DK, Jung YS, Kim HB, Kim YH, Yoo EK, *et al*. O-GlcNAcylation of Orphan Nuclear Receptor Estrogen-Related Receptor γ Promotes Hepatic Gluconeogenesis. *Diabetes* 2016;65(10):2835–2848. doi:10.2337/db15-1523, PMID:27335230.
- [42] Miao J, Xiao Z, Kanamalluru D, Min G, Yau PM, Veenstra TD, *et al*. Bile acid signaling pathways increase stability of Small Heterodimer Partner (SHP) by inhibiting ubiquitin-proteasomal degradation. *Genes Dev* 2009;23(8):986–996. doi:10.1101/gad.1773909, PMID:19390091.
- [43] Clifford BL, Sedgeman LR, Williams KJ, Morand P, Cheng A, Jarrett KE, *et al*. FXR activation protects against NAFLD via bile-acid-dependent reductions in lipid absorption. *Cell Metab* 2021;33(8):1671–1684.e1674. doi:10.1016/j.cmet.2021.06.012, PMID:34270928.
- [44] Yang ZX, Shen W, Sun H. Effects of nuclear receptor FXR on the regulation of liver lipid metabolism in patients with non-alcoholic fatty liver disease. *Hepatol Int* 2010;4(4):741–748. doi:10.1007/s12072-010-9202-6, PMID:21286345.
- [45] Zheng Y, Ying H, Shi J, Li L, Zhao Y. Alanyl-Glutamine Dipeptide Attenuates Non-Alcoholic Fatty Liver Disease Induced by a High-Fat Diet in Mice by Improving Gut Microbiota Dysbiosis. *Nutrients* 2023;15(18):3988. doi:10.3390/nu15183988, PMID:37764772.
- [46] Kim YC, Qi M, Dong X, Seok S, Sun H, Kemper B, *et al*. Transgenic mice lacking FGF15/19-SHP phosphorylation display altered bile acids and gut bacteria, promoting nonalcoholic fatty liver disease. *J Biol Chem* 2023;299(8):104946. doi:10.1016/j.jbc.2023.104946, PMID:37348559.
- [47] Huang J, Iqbal J, Saha PK, Liu J, Chan L, Hussain MM, *et al*. Molecular characterization of the role of orphan receptor small heterodimer partner in development of fatty liver. *Hepatology* 2007;46(1):147–157. doi:10.1002/hep.21632, PMID:17526026.
- [48] Watanabe M, Houten SM, Wang L, Moschetta A, Mangelsdorf DJ, Heyman RA, *et al*. Bile acids lower triglyceride levels via a pathway involving FXR, SHP, and SREBP-1c. *J Clin Invest* 2004;113(10):1408–1418. doi:10.1172/jci21025, PMID:15146238.
- [49] Brendel C, Schoonjans K, Botrugno OA, Treuter E, Auwerx J. The small heterodimer partner interacts with the liver X receptor α and represses its transcriptional activity. *Mol Endocrinol* 2002;16(9):2065–2076. doi:10.1210/me.2001-0194, PMID:12198243.
- [50] Zou A, Magee N, Deng F, Lehn S, Zhong C, Zhang Y. Hepatocyte nuclear receptor SHP suppresses inflammation and fibrosis in a mouse model of nonalcoholic steatohepatitis. *J Biol Chem* 2018;293(22):8656–8671. doi:10.1074/jbc.RA117.001653, PMID:29666185.
- [51] Lee YK, Park JE, Lee M, Mifflin R, Xu Y, Novak R, *et al*. Deletion of hepatic small heterodimer partner ameliorates development of nonalcoholic steatohepatitis in mice. *J Lipid Res* 2023;64(11):100454. doi:10.1016/j.jlr.2023.100454, PMID:37827334.
- [52] Mifflin R, Park JE, Lee M, Jena PK, Wan YY, Barton HA, *et al*. Microbial products linked to steatohepatitis are reduced by deletion of nuclear hormone receptor SHP in mice. *J Lipid Res* 2023;64(12):100469. doi:10.1016/j.jlr.2023.100469, PMID:37922990.
- [53] Na H, Lee H, Lee MH, Lim HJ, Kim HJ, Jeon Y, *et al*. Deletion of exons 3 and 4 in the mouse Nr1d1 gene worsens high-fat diet-induced hepatic steatosis. *Life Sci* 2016;166:13–19. doi:10.1016/j.lfs.2016.10.003, PMID:27720799.
- [54] Han YH, Shin KO, Kim JY, Khadka DB, Kim HJ, Lee YM, *et al*. A maresin 1/ROR α /12-lipoxygenase autoregulatory circuit prevents inflammation and progression of nonalcoholic steatohepatitis. *J Clin Invest* 2019;129(4):1684–1698. doi:10.1172/jci124219, PMID:30855276.
- [55] Roberts DR, Paine-Cabrera D, Kotulkar M, Venneman KK, Gunewardena S, Foquet L, *et al*. Identifying novel mechanisms of per- and polyfluoroalkyl substance-induced hepatotoxicity using FRG humanized mice. *Arch Toxicol* 2024;98(9):3063–3075. doi:10.1007/s00204-024-03789-0, PMID:38782768.
- [56] Gunewardena S, Huck I, Walesky C, Roberts D, Weinman S, Apte U. Progressive loss of hepatocyte nuclear factor 4 α activity in chronic liver diseases in humans. *Hepatology* 2022;76(2):372–386. doi:10.1002/hep.32326, PMID:35006629.
- [57] Kim HS, Yoon JS, Jeon Y, Park EJ, Lee JK, Chen S, *et al*. Ssu72-HNF4 α signaling axis classify the transition from steatohepatitis to hepatocellular carcinoma. *Cell Death Differ* 2022;29(3):600–613. doi:10.1038/s41418-021-00877-x, PMID:34616001.
- [58] Lee SH, Veeriah V, Levine F. Liver fat storage is controlled by HNF4 α through induction of lipophagy and is reversed by a potent HNF4 α agonist. *Cell Death Dis* 2021;12(6):603. doi:10.1038/s41419-021-03862-x, PMID:34117215.
- [59] Xu Y, Zhu Y, Hu S, Xu Y, Stroup D, Pan X, *et al*. Hepatocyte Nuclear Factor 4 α Prevents the Steatosis-to-NASH Progression by Regulating p53 and Bile Acid Signaling (in mice). *Hepatology* 2021;73(6):2251–2265. doi:10.1002/hep.31604, PMID:33098092.
- [60] Li Y, Zalzal M, Jadhav K, Xu Y, Kasumov T, Yin L, *et al*. Carboxylesterase 2 prevents liver steatosis by modulating lipolysis, endoplasmic reticulum stress, and lipogenesis and is regulated by hepatocyte nuclear factor 4 α in mice. *Hepatology* 2016;63(6):1860–1874. doi:10.1002/hep.28472, PMID:26806650.
- [61] Yang X, Fu Y, Hu F, Luo X, Hu J, Wang G. PI3K3R3 regulates PPAR α expression to stimulate fatty acid β -oxidation and decrease hepatosteatosis. *Exp Mol Med* 2018;50(1):e431. doi:10.1038/emmm.2017.243, PMID:29350678.
- [62] Kasano-Camones CI, Takizawa M, Ohshima N, Saito C, Iwasaki W, Nakagawa Y, *et al*. PPAR α activation partially drives NAFLD development in liver-specific Hnf4a-null mice. *J Biochem* 2023;173(5):393–411. doi:10.1093/jb/mvad005, PMID:36779417.
- [63] Jia N, Lin X, Ma S, Ge S, Mu S, Yang C, *et al*. Amelioration of hepatic steatosis is associated with modulation of gut microbiota and suppression of hepatic miR-34a in *Gynostemma pentaphyllum* (Thunb.) Makino treated mice. *Nutr Metab (Lond)* 2018;15:86. doi:10.1186/s12986-018-0323-6, PMID:30555521.
- [64] Yu D, Chen G, Pan M, Zhang J, He W, Liu Y, *et al*. High fat diet-induced oxidative stress blocks hepatocyte nuclear factor 4 α and leads to hepatic steatosis in mice. *J Cell Physiol* 2018;233(6):4770–4782. doi:10.1002/jcp.26270, PMID:29150932.
- [65] Song Y, Wu W, Sheng L, Jiang B, Li X, Cai K. Chrysin ameliorates hepatic steatosis induced by a diet deficient in methionine and choline by inducing the secretion of hepatocyte nuclear factor 4 α -dependent very low-density lipoprotein. *J Biochem Mol Toxicol* 2020;34(7):e22497. doi:10.1002/

- jbt.22497, PMID:32220030.
- [66] Crevet L, Vanacker JM. Regulation of the expression of the estrogen related receptors (ERRs). *Cell Mol Life Sci* 2020;77(22):4573–4579. doi:10.1007/s00018-020-03549-0, PMID:32448995.
- [67] Xia H, Dufour CR, Medkour Y, Scholtes C, Chen Y, Guluzian C, *et al*. Hepatocyte FBXW7-dependent activity of nutrient-sensing nuclear receptors controls systemic energy homeostasis and NASH progression in male mice. *Nat Commun* 2023;14(1):6982. doi:10.1038/s41467-023-42785-3, PMID:37914694.
- [68] B'Chir W, Dufour CR, Ouellet C, Yan M, Tam IS, Andrzejewski S, *et al*. Divergent Role of Estrogen-Related Receptor α in Lipid- and Fasting-Induced Hepatic Steatosis in Mice. *Endocrinology* 2018;159(5):2153–2164. doi:10.1210/en.2018-00115, PMID:29635284.
- [69] Liu D, Jia H, Holmes DI, Stannard A, Zachary I. Vascular endothelial growth factor-regulated gene expression in endothelial cells: KDR-mediated induction of Egr3 and the related nuclear receptors Nur77, Nurr1, and Nor1. *Arterioscler Thromb Vasc Biol* 2003;23(11):2002–2007. doi:10.1161/01.ATV.0000098644.03153.6f, PMID:14525795.
- [70] Veum VL, Dankel SN, Gjerde J, Nielsen HJ, Solsvik MH, Haugen C, *et al*. The nuclear receptors NUR77, NURR1 and NOR1 in obesity and during fat loss. *Int J Obes (Lond)* 2012;36(9):1195–1202. doi:10.1038/ijo.2011.240, PMID:22143616.
- [71] Yu X, Yang K, Fang Z, Liu C, Hui T, Guo Z, *et al*. Bioinformatics analysis of potential ferroptosis and non-alcoholic fatty liver disease biomarkers. *Gen Physiol Biophys* 2024;43(5):371–384. doi:10.4149/gpb_2024017, PMID:39140679.
- [72] Luo Z, Yan S, Chao Y, Shen M. Unveiling the mitophagy puzzle in non-alcoholic fatty liver disease (NAFLD): Six hub genes for early diagnosis and immune modulatory roles. *Heliyon* 2024;10(7):e28935. doi:10.1016/j.heliyon.2024.e28935, PMID:38601640.
- [73] Cao Y, Du Y, Jia W, Ding J, Yuan J, Zhang H, *et al*. Identification of biomarkers for the diagnosis of chronic kidney disease (CKD) with non-alcoholic fatty liver disease (NAFLD) by bioinformatics analysis and machine learning. *Front Endocrinol (Lausanne)* 2023;14:1125829. doi:10.3389/fendo.2023.1125829, PMID:36923221.
- [74] Yu R, Huang Y, Hu X, Chen J. Analysis of machine learning based integration to identify the crosslink between inflammation and immune response in non-alcoholic fatty liver disease through bioinformatic analysis. *Heliyon* 2024;10(14):e32783. doi:10.1016/j.heliyon.2024.e32783, PMID:39108890.
- [75] Nazari E, Khalili-Tanha G, Asadnia A, Pourali G, Maftooh M, Khazaei M, *et al*. Bioinformatics analysis and machine learning approach applied to the identification of novel key genes involved in non-alcoholic fatty liver disease. *Sci Rep* 2023;13(1):20489. doi:10.1038/s41598-023-46711-x, PMID:37993474.
- [76] Liang H, Xie X, Song X, Huang M, Su T, Chang X, *et al*. Orphan nuclear receptor NR4A1 suppresses hyperhomocysteinemia-induced hepatic steatosis in vitro and in vivo. *FEBS Lett* 2019;593(10):1061–1071. doi:10.1002/1873-3468.13384, PMID:30973961.
- [77] Fayard E, Auwerx J, Schoonjans K. LRH-1: an orphan nuclear receptor involved in development, metabolism and steroidogenesis. *Trends Cell Biol* 2004;14(5):250–260. doi:10.1016/j.tcb.2004.03.008, PMID:15130581.
- [78] Sun Y, Demagry H, Schoonjans K. Emerging functions of the nuclear receptor LRH-1 in liver physiology and pathology. *Biochim Biophys Acta Mol Basis Dis* 2021;1867(8):166145. doi:10.1016/j.bbdis.2021.166145, PMID:33862147.
- [79] Sahini N, Borlak J. Genomics of human fatty liver disease reveal mechanistically linked lipid droplet-associated gene regulations in bland steatosis and nonalcoholic steatohepatitis. *Transl Res* 2016;177:41–69. doi:10.1016/j.trsl.2016.06.003, PMID:27376874.
- [80] Sánchez V, Baumann A, Brandt A, Wodak MF, Staltner R, Bergheim I. Oral Supplementation of Phosphatidylcholine Attenuates the Onset of a Diet-Induced Metabolic Dysfunction-Associated Steatohepatitis in Female C57BL/6J Mice. *Cell Mol Gastroenterol Hepatol* 2024;17(5):785–800. doi:10.1016/j.jcmgh.2024.01.009, PMID:38262589.
- [81] Lee JM, Lee YK, Mamrosh JL, Busby SA, Griffin PR, Pathak MC, *et al*. A nuclear-receptor-dependent phosphatidylcholine pathway with antidiabetic effects. *Nature* 2011;474(7352):506–510. doi:10.1038/nature10111, PMID:21614002.
- [82] Lee JS, Bae S, Kang HS, Im SS, Moon YA. Liver receptor homolog-1 regulates mouse superoxide dismutase 2. *Biochem Biophys Res Commun* 2017;489(3):299–304. doi:10.1016/j.bbrc.2017.05.144, PMID:28552526.
- [83] Oiwa A, Kakizawa T, Miyamoto T, Yamashita K, Jiang W, Takeda T, *et al*. Synergistic regulation of the mouse orphan nuclear receptor SHP gene promoter by CLOCK-BMAL1 and LRH-1. *Biochem Biophys Res Commun* 2007;353(4):895–901. doi:10.1016/j.bbrc.2006.12.131, PMID:17204240.
- [84] Wang S, Sheng F, Zou L, Xiao J, Li P. Hyperoside attenuates non-alcoholic fatty liver disease in rats via cholesterol metabolism and bile acid metabolism. *J Adv Res* 2021;34:109–122. doi:10.1016/j.jare.2021.06.001, PMID:35024184.
- [85] Luo L, Zhang H, Chen W, Zheng Z, He Z, Wang H, *et al*. Angelica sinensis polysaccharide ameliorates nonalcoholic fatty liver disease via restoring estrogen-related receptor α expression in liver. *Phytother Res* 2023;37(11):5407–5417. doi:10.1002/ptr.7982, PMID:37563852.
- [86] Peng A, Liu S, Fang L, Zhu Z, Zhou Y, Yue S, *et al*. Inonotus obliquus and its bioactive compounds alleviate non-alcoholic fatty liver disease via regulating FXR/SHP/SREBP-1c axis. *Eur J Pharmacol* 2022;921:174841. doi:10.1016/j.ejphar.2022.174841, PMID:35278405.
- [87] Mao L, Peng L, Ren X, Chu Y, Nie T, Lin W, *et al*. Discovery of JND003 as a New Selective Estrogen-Related Receptor α Agonist Alleviating Nonalcoholic Fatty Liver Disease and Insulin Resistance. *ACS Bio Med Chem Au* 2022;2(3):282–296. doi:10.1021/acsbiochemchem.1c00050, PMID:35874496.
- [88] Dhillon S. Dapagliflozin: A Review in Type 2 Diabetes. *Drugs* 2019;79(10):1135–1146. doi:10.1007/s40265-019-01148-3, PMID:31236801.
- [89] Qiao P, Jia Y, Ma A, He J, Shao C, Li X, *et al*. Dapagliflozin protects against nonalcoholic steatohepatitis in db/db mice. *Front Pharmacol* 2022;13:934136. doi:10.3389/fphar.2022.934136, PMID:36059948.