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Targeting nuclear receptors for NASH/MASH: From bench to bedside*

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Abstract

The onset of metabolic dysfunction-associated steatohepatitis (MASH) or non-alcoholic steatohepatitis (NASH) represents a tipping point leading to liver injury and subsequent hepatic complications in the natural progression of what is now termed metabolic dysfunction-associated steatotic liver diseases (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD). With no pharmacological treatment currently available for MASH/NASH, the race is on to develop drugs targeting multiple facets of hepatic metabolism, inflammation, and pro-fibrotic events, which are major drivers of MASH. Nuclear receptors (NRs) regulate genomic transcription upon binding to lipophilic ligands and govern multiple aspects of liver metabolism and inflammation. Ligands of NRs may include hormones, lipids, bile acids, and synthetic ligands, which upon binding to NRs regulate the transcriptional activities of target genes. NR ligands are presently the most promising drug candidates expected to receive approval from the United States Food and Drug Administration as a pharmacological treatment for MASH. This review aims to cover the current understanding of NRs, including nuclear hormone receptors, non-steroid hormone receptors, circadian NRs, and orphan NRs, which are currently undergoing clinical trials for MASH treatment, along with NRs that have shown promising results in preclinical studies.

Keywords

Nuclear receptor (NR); Metabolic dysfunction-associated steatohepatitis (MASH); Metabolic dysfunction-associated steatotic liver disease (MASLD); Transcription factor; Liver; Drug

1 Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD)/non-alcoholic fatty liver disease (NAFLD) is one of the fastest-growing metabolic epidemics worldwide.[1] A

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recent study published in 2023, shows an overall global prevalence of MASLD around 30.05% with an approximate increase of 50.4% from 25.26% in 1990−2006 to 38.2% in 2016−2019.[2] Metabolic dysfunctionassociated steatohepatitis (MASH) is a clinically advanced stage of MASLD, and is a risk factor for several end-stage liver diseases.[3] MASH is now recognized as a major cause for liver transplantation and is often associated with diabetes and chronic kidney disease.[4,5] It is triggered by decompensated steatosis in hepatocytes upon fatty acid and sugar influx, resulting in hepatocyte injury via a process termed “Lipotoxicity”.[6] Decompensated steatosis results in the increased availability of free fatty acids in the hepatocyte cytosol, leading to lipotoxic injury by inducing mitochondrial damage, oxidative stress, endoplasmic reticulum stress, and eventually resulting in hepatocyte death. The injured or dying hepatocytes release several damage-associated molecular patterns (DAMPs), which upon binding to DAMP receptors on macrophages and hepatic stellate cells (HSCs), trigger these cells to adopt an activated phenotype, thereby leading to inflammation and fibrosis in the liver, which is a hallmark of MASH.[7,8] Presently, there are no approved pharmacological treatments for MASH, and lifestyle modification remains the sole available option for its management. This review outlines the current understanding of nuclear receptors (NRs) function in the liver, their dysregulation in MASH, and the therapeutic targeting to counter MASH pathogenesis.

2 NRs pharmacology and its application in MASH treatment

Phenotypic alteration of hepatocytes in MASH is a result of dynamic changes in the transcriptome in response to extracellular cues, including nutrients, hormones, and cytokines. NRs, a ligand-regulated class of transcription factors, play a critical role as key mediators of hepatic transcriptome alteration in response to environmental stress. NRs act as ligand-activated transcriptional regulators that affect hepatic pathophysiology. In humans, 48 NRs have been defined by shared structural and functional features, including DNA-binding domains and ligand-binding domains. Among these, four classes of NRs play key roles in regulating liver metabolism. Targeting these receptors has shown preclinical and/or clinical efficacy in modulating MASH pathology.[9] The first class of these NRs includes the classical hormone receptors, such as thyroid hormone receptor (THR), glucocorticoid receptor (GR), estrogen receptor (ER), vitamin D receptor (VDR), and retinoic acid receptor (RAR). The second class of NRs are non-steroid hormone receptors that are activated by lipids or their derivatives. It includes peroxisome proliferator-activated receptors (PPARs), farnesoid X receptor (FXR), liver X receptor (LXR), and pregnane X receptor (PXR), which mainly utilize dietary lipids as their ligands. The third group contains REV-ERBs and RAR-related orphan receptors (RORs) that regulate the temporal transcription of liver metabolic genes aligned with the circadian rhythm. Lastly, the fourth class of NRs includes the “orphan receptors” the endogenous ligands of which remain unidentified and include estrogen-related receptor (ERR), constitutive androstane receptor (CAR), small heterodimer partner (SHP), hepatocyte nuclear factor 4 alpha (HNF4α), and liver receptor homolog-1 (LRH-1/NR5A2). In the liver, several hormones and lipid-induced NRs heterodimerize with retinoid X receptors (RXRs) and mediate the epigenetic modulation of gene transcription upon binding to hormone response elements on the target gene promoter or enhancer region (Fig. 1).[10] Besides their classical genomic action, several non-genomic actions of NRs

have been described; however, their relative contribution to human physiology remains less elucidated.[11] Several genes (*e.g.*, PPARα, PPAR γ, NRH14) involved in lipid and glucose metabolism, inflammation, and fibrosis are targets of NRs in the liver (Fig. 2). Therefore, NRs have been at the forefront of targeting strategies for MASH, targeting different stages of MASH progression by affecting lipid and bile metabolism, activating immune cell, and modulating pro-fibrotic signaling.

3 Nuclear hormone receptors and MASH

Hormone-responsive NRs regulate different aspects of hepatic lipid and glucose metabolism. Studies performed in both animals and humans have shown that alterations in hormones and their cognate NRs are associated with both the incidence and progression of MASLD and MASH. Furthermore, hormones and hormone mimetics have shown efficacy in resolving MASH severity in both preclinical and clinical studies as described below.

3.1 THRs

THRs are nuclear resident transcription factors that bind to thyroid hormone (TH) and triiodothyronine (T_3), regulating the expression of several genes involved in lipogenesis, fat-oxidation, cholesterol transport, and gluconeogenesis in the liver.[12] In humans and rodents, two THRs (THRalpha (THRα) and THRbeta (THRβ)) are expressed, with THRβ being the predominant form in the liver. Once inside the nuclei, T_3 may activate or repress the expression of its target genes through the action of its receptor bound to the DNA.[13] T_3-induced genes harbor a cognate DNA sequence in their promoter/enhancer regions known as positive thyroid response elements (TRE), on which T_3 bound THR complex is recruited either as a homodimer or as a heterodimer with RXR. The presence of T_3 leads to the assembly of a THR-coactivator complex with an intrinsic histone acetylase activity resulting in nucleosome uncoiling and RNA POL II-mediated transcription.[13] In the liver, THRs are expressed in hepatocytes, cholangiocytes, kupffer cells, and HSCs, and therefore, TH can influence almost all aspects of hepatic physiology.[14–17] Epidemiological studies have shown an increased incidence of MASLD with both overt and subclinical hypothyroidism in humans.[18–23] Furthermore, animal models of MASH have shown evidence of intra-hepatic TH insufficiency, suggesting deregulated TH metabolism in fatty liver.[24] In rodent models of diet-induced MASH, both T_3 and the liver-specific THRβ agonist significantly reduced hepatic steatosis and inflammation.[25–27] At a molecular level, T_3 decreases MASLD/MASH by increasing mitochondrial β-oxidation and promoting autophagy in the hepatocytes.[12,28–32] Further evidence supporting the role of THRs in MASLD comes from a mouse model that expresses a dominant negative mutation in THRβ (THR$\beta^{PV/PV}$). These mutant mice develop hepatosteatosis by 4–5 months of age.[33] Similarly, humans with a similar mutation in THRβ, characterized as resistance to thyroid hormone (RTH) phenotype, also exhibit increased hepatic fat content.[34] In human studies, low-dose TH as well as two liver-specific THRβ specific agonists VK-2809/MB-07811 and resmetirom (MGL-3196) have shown significant efficacy in resolving MASLD/MASH.[35,36] The pivotal phase 3 MAESTRO-NASH clinical trial with Madrigal Pharmaceuticals' oral MASH therapy, resmetirom, robustly demonstrated a significant reduction in hepatic fat and inflammation in patients

with MASH. This treatment has received the United States Food and Drug Administration (FDA) breakthrough therapy designation.[37–41]

3.2 GRs

Hepatic genes related to glucose homeostasis, stress response, and inflammation, are regulated by GRs. GRs can be activated by both endogenous steroids (*e.g.*, cortisol) and pharmaceutical ligands such as dexamethasone. At a molecular level, ligand binding to the cytoplasmic GRs elicits a conformational change in GRs and their interaction with the chaperone complex, which aids in GRs translocation into the nucleus.[42] Upon entering the nucleus, GRs bind to DNA sequences known as glucocorticoid responsive elements (GRE) to activate or repress gene transcription. GRs can transactivate genes by binding to GRE as a dimer, but also as a monomer by binding to other transcription factors (TFs) through tethering or by binding to composite elements.[42] GRs may also heterodimerize with other NRs such as cyclic adenosine monophosphate (cAMP) response element binding protein (CREB) and peroxisome proliferator-activated receptor α (PPARα) during fasting to increase the expression of gluconeogenic and ketogenic genes in the liver.[43] Mouse models with liver-specific loss of GRs in obesity-prone animals (*db/db* mice) have shown amelioration of hepatic steatosis via derepression of the direct GR target gene, hairy enhancer of split 1 (*Hes1*).[44] In contrast, the loss of GRs in liver macrophages aggravated liver inflammation in animal models of obesity via repression of the anti-inflammatory glucocorticoid-induced leucine zipper (GILZ) expression in monocytes/macrophages.[45] However, steroids are known to induce fatty liver in humans, which has so far dampened any interest in targeting GRs for MASH.[46] Nevertheless, given the potential of glucocorticoids in ameliorating inflammation in MASH, clinical studies targeting GRs as a single adjuvant therapy in advance of MASH, are warranted.

3.3 ERs

Estrogens are a group of hormones essential for the development and function of the female reproductive system. The classic estrogenic hormone, estradiol (E_2) action is mediated by the ERs, which are expressed as ERα and ERβ isoforms.[47] ERα is the major isoform expressed in the liver and regulates the expression of several lipogenic genes.[48] Upon binding of the ligand, ERs dissociate from cytoplasmic heat shock protein 90 (HSP90) and translocate to the nucleus, where they bind to estrogen response elements (EREs) on the promoter region of the target genes.[47] In the liver, several other NRs, including the SHP and signal transducer and activator of transcription 3 (STAT3), are direct targets of ERα. Beneficial effects of E_2 on the liver, including the repression of lipid biosynthesis and gluconeogenesis, may be indirectly mediated by these secondary NRs.[49,50] The loss of ERα is known to induce hepatosteatosis in both male and female mice; however, extrahepatic ER signaling also contributes to the overall beneficial effects of E_2 on reducing hepatosteatosis.[51–55] Furthermore, ERα is essential for the protective effect of E_2 by inducing M1 to M2 macrophage polarization, thereby reducing MASH-associated inflammation in mice.[56] In humans, premenopausal females are less likely to develop MASLD compared to males; however, the risk of developing MASLD/MASH significantly increases in post-menopausal females.[57–60] Estrogen replacement therapy has also been found to mitigate the development of MASLD in diabetic patients.[61] These studies

suggest a protective role of estrogen and ERα against MASLD development in humans.[62] Additionally, ERα levels are shown to be reduced in the livers of MASH patients.[63] While ERα is more widely studied and expressed in various tissues including the liver, ERβ agonists have also shown protective effects in preclinical models of MASH.[64] Although clinical trials aimed at targeting ERs for MASH are currently lacking, preclinical studies are suggestive of perhaps testing this possibility in the future.

3.4 VDRs

While VDRs mediate the biological effects of vitamin D on the human skeletal system,[65] the extra-skeletal effects of vitamin D, particularly on MASLD progression, have been increasingly recognized.[66] The biologically active form of vitamin D is 1, 25-dihydroxyvitamin D3 ($1,25(OH)_2D_3$), which upon binding to VDR converts DNA-bound VDR homodimers into VDR-RXR heterodimers, which recruit corepressors or coactivators to regulate gene transcription.[65] In rodent models, animals treated with $1,25(OH)_2D_3$, displayed significant protection from diet-induced liver steatosis, inflammation, and fibrosis.[67–69] However, animal studies investigating the impact of vitamin D and VDRs on the progression of MASLD and MASH have yielded conflicting results. While some studies reported that VDR-deficient mice are resistant to high-fat diet (HFD)-induced or *ob/ob* model-induced liver steatosis and VDR-dependent steatosis, other long-term studies reported that the absence of VDRs can actually exacerbate hepatic inflammation and fibrosis.[70–73] While some studies have suggested the potential benefits of vitamin D in mitigating hepatic steatosis, the evidence is not conclusive. Conflicting data also stem from the diverse and opposing effects of liver, adipose, and intestinal VDRs in the regulation of hepatic steatosis.[73–76] Although expressed at a low level in hepatocytes, VDRs are enriched in non-parenchymal liver cells such as cholangiocytes, kupffer cells, and HSCs.[77] The VDR agonist $1,25(OH)_2D_3$ can ameliorate transforming growth factor-β1(TGF-β1)-induced stellate cell activation *in vitro*, and HFD-induced liver steatosis and inflammation *in vivo*.[73] Similarly, the activation of liver macrophage VDRs by vitamin D ameliorates liver inflammation, steatosis, and insulin resistance in mice.[78] In humans, VDR polymorphisms and circulating vitamin D levels have been associated with the severity of MASLD.[79–82] Human studies suggest that although hepatic VDR expression is upregulated in benign steatosis, it is only modestly increased in individuals with MASH, indicating a temporal effect of VDR function in MASLD progression, in a tissue/cell-type specific manner.[70] However, as the role of VDRs vis à vis that of vitamin D in MASH is still debatable and unclear, there are currently no clinical trials targeting VDR for the treatment of MASLD/MASH.

3.5 RARs

The RARs (RARα, RARβ, and RAR gamma (RARγ)) are ligand-activated transcription factors that are activated by both all-trans retinoic acid and 9-cis retinoic acid, retinoid active derivatives of vitamin A.[83] Like other NRs, RARs also heterodimerize with the RXRs and bind to their cognate sequences on the target gene promoter regions, thereby regulating transcription.[83] Endogenous retinoids regulate hepatic lipid and bile metabolism by binding to RARs.[84,85] Animal studies have demonstrated a protective effect of both all-trans retinoic acid administration and RARα over-expression in reducing hepatic steatosis.[86] Similarly, the over-expression of a dominant negative RARα, specifically in the liver,

exhibits steatohepatitis and insulin resistance in mice.[87] Furthermore, synthetic agonists for RARβ2 have shown efficacy in reducing hepatic lipid accumulation, activating HSCs, and alleviating insulin resistance in both genetic and diet-induced models of diabetes-associated MASLD.[88–90] Although perturbed retinoic acid metabolism is observed in MASLD and MASH patients, clinical trials utilizing RAR-targeted ligands for MASLD/MASH treatment are still lacking.[91,92] Intriguingly, in addition to retinoids, a novel synthetic RXR ligand, UAB126 (rexinoids), has shown positive results in preventing obesity-induced metabolic diseases, including MASLD, in animals fed obesogenic diets. Importantly, these effects were achieved without any adverse side effects including hyper-triglyceridemia, hepatomegaly, and disturbances in the thyroid hormone axis.[93] Thus, these results raise hopes of translating some promising leads obtained from retinoids and rexinoids into human clinical trials for MASLD.

4 Non-steroid hormone receptors

Non-steroid hormone NRs are activated by lipids, cholesterol, carbohydrates, and bile acids, and serve as a nutrient sensor within the cell. Many of these NRs, which belong to the class of non-steroid hormone receptors, are currently being considered, or already in clinical trials, to explore their efficacy in treating MASLD/MASH.[94–96]

4.1 PPARs

PPARs are lipid-regulated NRs that bind to PPAR response elements (PPREs) as heterodimers with RXRs, regulating the expression of genes involved in hepatic lipid and carbohydrate metabolism, inflammation, and cellular proliferation.[97] There are three PPAR isotypes: PPARα (NR1C1), PPARβ/delta(δ) (NR1C2), and PPARγ (NR1C3). Several ligands of PPARs, such as elafibranor, are currently under clinical development for the treatment of MASH.[98]

4.1.1 PPARα (NR1C1)—PPARα is a fasting-induced NR that directly regulates the genes involved in fatty acid uptake, lipophagy, β-oxidation, and ketogenesis within hepatocytes.[99–101] Additionally, some of the effects of PPARα are indirectly mediated via its induction of fibroblast growth factor 21 (FGF21), which increases lipid catabolism.[102] PPARα fasting knock-out mice show impaired fatty acid oxidation and hepatic fat accumulation.[103] Paradoxically, PPARα also increases the expression of lipogenic genes in the liver.[104] This conflicting effect of PPARα may be attributed to its differential preference for promoting lipolytic gene expression during fasting and lipogenesis in the fed state. Studies in PPAR null mice fed an HFD exhibit massive hepatic lipid accumulation owing to the inhibition of fatty acid uptake and β-oxidation.[105]

Moreover, PPARα shows an anti-inflammatory activity in a murine model of systemic inflammation.[106] In animal models of MASH, the PPARα agonist WY-14643 prevents hepatic steatosis and inflammation by reducing the number of activated macrophages and HSCs, ultimately facilitating the normalization of the histologic changes typical of MASH.[107] Furthermore, PPARα inhibits the fibrotic and inflammatory gene expression induced by MASH diets through its physical interaction with nuclear factor-kappa B and activator protein-1 transcription factors.[108,109] In humans, PPARα expression negatively

correlates with MASH severity.[110] A clinical trial using pemafibrate, a selective PPARα modulator, demonstrated improvement in magnetic resonance elastography-based liver stiffness and alanine transaminase (ALT) levels among patients with MASLD, but did not show a significant reduction in hepatic steatosis.[111] Similarly, a dual PPARα/δ agonist, elafibranor, also showed promise as an anti-MASH therapy in earlier studies but failed in the later phase III trials due to safety concerns.[112] Notably, pegozafermin which is an FGF-21 analogue has exhibited improvements in MASH-associated fibrosis during a recent phase II clinical trial, suggesting the potential of downstream PPARα signaling as a viable therapeutic area in MASH treatment.[113]

4.1.2 PPAR β/δ (NR1C2)—The activation of PPARβ/δ in hepatocytes increases the expression of the enzyme stearoyl-coenzyme A desaturase 1 (SCD1) that converts lipotoxic saturated fatty acids into mono-unsaturated fatty acids (MUFA), which can be easily stored as lipid droplets.[114] Indeed, animals with liver-specific adenovirus-mediated PPARβ/δ overexpression exhibit lesser hepatic damage, despite increased lipid accumulation when fed a diet rich in saturated fat.[115] A mechanism through which PPARβ/δ activation shows protection against MASLD is via the regulation of hepatic very low-density lipoprotein receptor (VLDLR).[116] Consistent with animal studies, the expression of VLDLR correlates negatively with the abundance of PPARβ/δ in steatotic liver biopsy specimens.[116 112]

4.1.3 PPAR γ (NR1C3)—While expressed at a very low level in the liver, PPARγ is induced in the livers of animals upon feeding an HFD.[117] Concurrently, hepatic ablation of PPARγ prevents the development of hepatic steatosis by reducing both hepatic fatty acid uptake and DNL.[118,119] Paradoxically, the administration of PPARγ ligand rosiglitazone ameliorates the MASH phenotype in animal models.[120] This paradoxical effect of PPARγ is likely mediated by its differential effect on HSCs *vs.* hepatocytes. Indeed, the activated profibrotic phenotype of HSCs may be reversed to the quiescent ones upon binding PPARγ ligands, thus highlighting PPARγ ability to modulate pro-inflammatory and pro-fibrogenic gene expression in HSCs.[121–124] Additionally, PPARγ acts in liver macrophages to induce M2-type polarization, which is associated with decreased secretion of inflammatory cytokines and growth factors, thereby resulting in attenuated fibrosis.[125–127] Indeed, macrophage-specific PPARγ deletion predisposes animals to develop diet-induced obesity and insulin resistance and worsen carbon tetrachloride-induced liver fibrosis.[128] Similarly to rodents, PPARγ expression is also increased in the human steatotic liver.[129] PPARγ agonists, including rosiglitazone and pioglitazone, have been evaluated in several clinical trials, showing efficacy in alleviating steatosis and inflammation, but with a modest reduction of fibrosis.[130–132] However, a PPARα/γ dual agonist, saroglitazar, has exhibited significant efficacy in resolving MASH and is currently an approved drug for MASH treatment in India.[133]

Recently, a phase III clinical trial led by Inventiva Pharma is underway to evaluate the efficacy of a pan-PPAR agonist lanifibranor in MASH (ClinicalTrials.gov, NCT04849728). Results from the prior phase IIb trial showed a significant improvement in MASH resolution with lanifibranor.[134]

4.2 FXR

FXR is a bile acid receptor that regulates the metabolism of bile, lipids, and carbohydrates.[135] FXR is highly expressed in the liver, brain, intestine, and kidney, and it exerts profound metabolic effects.[136] FXR heterodimerizes with RXR and binds to inverted repeats with 1 nucleotide separating (IR1).[135] The natural ligands of FXR, including chenodeoxycholic acid (CDCA) and cholic acid (CA), facilitate the recruitment of coactivators and the upregulation of transcription.[135] The systemic activation of FXR by a synthetic agonist (GW4064) and obeticholic acid (OCA) improved glucose tolerance and ameliorated steatosis severity in mice fed with an HFD and high carbohydrate diet.[137,138] In another mouse model of MASH, administration with FXR ligand WAY-362450 for 4 weeks, led to decreased levels of liver enzymes, reduced inflammatory cell infiltration, and alleviated hepatic steatosis, all of which were dependent on FXR expression.[139] More recently, a study has demonstrated that the FXR agonist GSK2324 regulates hepatic lipids by reducing absorption and selectively decreasing fatty acid synthesis via its distinct effect on intestinal and hepatic FXRs.[140] In the liver, FXR negatively regulates lipogenesis and positively enhances β-oxidation via its induction of SHP and PPARα.[141,142] Furthermore, FXR sulfhydration affected by hepatic endogenous H_2S promotes FXR activity and attenuates MASLD.[143] Notably, although FXR expression is low in HSCs, its anti-fibrotic action is presumed to be executed by FGF-19/15, which is responsive to intestinal FXR activation.[144–146]

In a multicenter, randomized, phase III study, the FXR ligand OCA, demonstrated improved liver histology, including improvements in steatosis, inflammation, and fibrosis (measured as NAFLD activity score), in non-cirrhotic, non-alcoholic steatohepatitis patients within the farnesoid X receptor ligand obeticholic acid in NASH treatment (FLINT) trial; however, further clarification is needed regarding its long-term benefits and safety.[147] Similarly, in a phase III, randomized, double-blind, placebo-controlled trial known as REGENERATE (ClinicalTrials.gov, NCT02548351), notable improvements in significantly improved fibrosis and key components of MASH disease activity were observed among patients with MASH.[148] However, two recent trials, REVERSE (ClinicalTrials.gov, NCT03439254) and OCALIVA evaluating the efficacy of OCA failed to reach expected MASH endpoints in terms of statistical significance for histological improvement. Several nonsteroidal FXR agonists (tropifexor, nidufexor, and turofexorate) are also in the trial pipeline for MASH treatment. Recently, a phase II trial on GS-9674 (cilofexor), an FXR agonist showed improvement in hepatic steatosis, liver biochemistry, and serum bile acids, in patients with MASH (ClinicalTrials.gov, NCT02854605). Similarly, the reduction in ALT levels and hepatic fat induced by tropifexor was sustained up to week 48 (ClinicalTrials.gov, NCT02855164); however, dose-related pruritus was frequently observed.[149] In spite of mixed success, FXR agonists remain an attractive choice for future MASH therapy.

4.3 LXRs

LXRs are cholesterol sensors that play a crucial role in regulating fatty acids, sphingolipids, cholesterol, and glucose metabolism, as well as inflammation.[150–152] LXRs exist as two isotypes: LXRα is expressed mainly in the liver, adipose tissue, kidney, and macrophages, whereas LXRβ is expressed ubiquitously.[151,152] Natural ligands of LXRs include oxysterols

(cholesterol derivatives) such as 24(S),25-epoxycholesterol, 25-hydroxycholesterol, and 22(R)-hydroxycholesterol. Upon ligand binding, nuclear LXRs heterodimerize with RXRs to regulate the expression of hepatic genes involved in DNL (*FASN, SREBP1c, SCD1)* and cholesterol excretion (*CYP7A1,* ATP-binding cassette transporters A1*(ABCA1) and ABCG1).*[151,152] Although the activation of LXRs in mouse hepatocytes increases hepatic steatosis when challenged with saturated fats, this process serves as a cytoprotective mechanism by converting saturated fats into MUFAs through the action of LXR target gene SCD1.[153] Following LXR agonist treatment, LXRs exert anti-inflammatory functions via suppression of pro-inflammatory genes such as cyclooxygenase-2 (COX-2) and inducible NO synthase (iNOS).[154] Additionally, LXR activation inhibits Toll-like receptor (TLR) ligand dependent inflammatory pathways through ABCA1 induction in macrophages.[155] In mice deficient in LXRα, feeding a high-cholesterol diet promoted cholesterol accumulation and increased serum levels of ALT and aspartate aminotransferase (AST), as well as enhanced macrophage recruitment and Kupffer cell activation.[156] Furthermore, LXRα/β double knockout mice show hepatic fibrosis, evidenced by the accumulation of hepatic lipid droplets and the induction of pro-fibrotic genes such as *Acta2* and *Col1a1*.[157] As LXR levels in humans positively correlate with MASLD severity and exhibit cell type specific pleiotropic effects on steatosis and inflammation.[158] However, no clinical trials with either LXR antagonist or agonist are currently ongoing. Future research is needed to better understand the complex mechanisms of LXR signaling in MASLD and to optimize therapeutic strategies targeting LXRs.

4.4 PXR

The xenobiotic sensor PXR acts as a receptor for endobiotics, including bile acids, cholesterol, and steroid derivatives in the liver.[159] Animal studies have shown that PXR activation in diet-induced MASH mouse models promotes a “fatty phenotype”.[160,161] Consistently, a reduction in HFD-induced obesity was observed in PXR knockout mice and was correlated with an upregulation of FGF15 expression, which suppresses the synthesis of bile acids and reduces lipid absorption and triglycerides (TGs) in the liver.[162] However, PXR levels have been shown to be down-regulated in human MASH.[163] Therefore, given the discordance in the data regarding the role of PXR in human *vs.* mouse MASLD, further studies are still required to elucidate its utility in targeting MASH.[164]

5 Circadian NRs

5.1 REV-ERBs

The REV-ERB proteins, which exist in REV-ERBα and REV-ERBβ isoforms, mediate the negative feedback loop of the circadian clock in mammals.[165] These NRs bind heme as their natural ligand and act as a transcriptional repressor of several metabolic genes in the liver.[165] The combined loss of both REV-ERB isoforms results in hepatosteatosis in mice.[166] Similarly, treatment with REV-ERB panagonists modifies both CLOCK and metabolic gene expression, reduces hepatic TG storage, and suppresses hepatic cholesterol synthesis in a diet-induced mouse MASLD model.[167] Another study using a high-calorie diet fed genetically obese mice showed that REV-ERB pan-agonists inhibited fibrosis, suggesting a direct role of REV-ERBs in regulating MASLD/MASH pathogenesis.[168,169] REV-ERBs

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also regulate different facets of liver inflammation, including inflammasome activation and T-helper 17 (Th17) cell activation, which are key players in MASH progression.[168] Although a putative REV-ERB agonist SR9009 is available as a dietary supplement, there are no ongoing clinical trials targeting REV-ERB for MASLD/MASH therapy. Despite the potential benefits of targeting REV-ERBs in MASH, further research is needed to fully elucidate their mechanism of action and evaluate their efficacy and safety in clinical settings.

5.2 RORs

In contrast to REV-ERBs, RORs mostly act as transcriptional activators, and coordinate the circadian rhythms of lipid metabolism and inflammation in the liver.[170] RORα and RORγ are the predominant RORs expressed in the liver and can be activated by cholesterol derivatives.[171] The RORs play a critical role in orchestrating the circadian synchronization of hepatic lipid metabolism. Notably, a significant elevation in hepatic TG levels was observed in hepatic-specific RORα knockout mice fed an HFD.[172–175] The action of RORs on immune cells also regulates liver inflammation in MASH.[176] However, given the puzzling results obtained from synthetic agonists and inverse agonists of RORs in mouse models of MASH, more work needs to be done before considering any clinical trial.[176–178]

6 Orphan NRs

By definition, an orphan NR is a protein that shares a structural similarity with identified receptors, but whose endogenous ligand remains unknown. Nevertheless, their genetic silencing and modulation by synthetic ligands demonstrate their vital role in regulating metabolic functions.

6.1 ERRs

ERRs are key regulators of energy metabolism and mediate mitochondrial oxidative metabolism.[179] ERRα, the predominant isoform expressed in the liver induces or represses target gene expression by interaction with coregulators such as peroxisome proliferator-activated receptor-gamma coactivator-1α (PGC-1α).[179] Metabolic crosstalk with other NRs such as PPARs, and THRs affect different aspects of ERRα metabolic signaling.[180] Studies employing whole-body ERRα knockout models have shown resistance to HFD-induced weight gain.[181] However, in contrast, the loss of ERRα aggravated the mammalian target of rapamycin inhibition induced fatty liver in mice.[182] Similarly, the lack of ERRα exhibited differential effects on lipid-induced and fasting-induced hepatic steatosis in mice.[183] Additionally, hepatic VLDL-TG secretion is blunted in ERRα liver-specific knockout mice, leading to hepatosteatosis, cellular stress, inflammation, and MASH development. Importantly, ERRα acts downstream of estrogen/ERα signaling, contributing to sex-based differences in MASLD/MASH.[184] Recently, the utilization of small molecule inhibitors of ERRα has shown promise in diminishing hepatic lipid deposition and MASH development in both dietary and genetic models of MASLD.[185] Collectively, there seems to be discordance in the results obtained from various studies, which may be attributed to the tissue-specific effect of ERRα. Further resolution of ERRα inhibition *vs.* activation using liver specificity of ERRα targeting modulators may pave the way for human trials in MASH.

6.2 CAR

Originally identified as an NR that regulates drug metabolism and detoxification, CAR has recently been recognized to be associated with energy metabolism and is found to be abundantly expressed in the liver.[186] Studies conducted in mice have shown that CAR activation directly leads to liver steatosis, and its genetic ablation protects from diet-induced as well as toxicant-induced MASH.[187–190] However, in contrast, other studies have demonstrated that the loss of CAR actually worsens MASLD and MASH-induced fibrosis in mice.[191,192] Additionally, CAR levels were found to be negatively correlated with MASH severity in humans.[193] Thus, the relationship between CAR and MASLD/MASH should be further assessed, and there are currently no therapies targeting CAR in clinical trials.

6.3 SHP

Predominantly expressed in the liver, SHP is an atypical NR that lacks a DNA-binding domain.[194] SHP acts as a repressor of NR action by competing for the coactivators required for NR action.[195] In the liver, the role of SHP remains controversial, with studies showing totally contrasting effects of SHP modulation on the development of steatosis and inflammation in animals with pro-steatotic *vs.* anti-inflammatory effects.[196–202] Furthermore, a notable reduction in SHP levels has been observed in patients at the advanced stages compared to those in mild MASLD, suggesting a stage-specific function of SHP during MASLD development.[203] Given the unclear function of SHP in MASLD development, no clinical trials are currently underway.

6.4 HNF4α

HNF4α, unlike SHP, acts as a transcriptional activator that drives the transcription of a broad spectrum of genes related to essential liver functions involving lipid, glucose, drug, and bile acid metabolism, as well as inflammatory response. HNF4α activation has also been linked to improvements in MASH pathology, while the loss of HNF4α activity leads to hepatic steatosis and MASH progression.[204–209] Additionally, a chemical antagonist of HNF4α was shown to induce hepatic steatosis in mice.[210] Given the beneficial role of HNF4α in MASH prevention and its down-regulation observed in human MASH, clinical trials involving HNF4α activators may be an attractive possibility for MASH treatment.[211]

6.5 LRH-1/NR5A2

LRH-1/NR5A2, originally identified in the liver as a regulator of bile acid and cholesterol homeostasis, regulates a multitude of other hepatic metabolic processes, encompassing glucose and lipid processing, methyl group sensing, and cellular stress responses.[212] Studies performed in liver-specific LRH-1 null mice unveiled derangement in phospholipid composition, hepatic steatosis, and the development of MASH phenotype.[213] Furthermore, LRH-1 levels were found to decrease as MASH progressed in humans. Given the encouraging results from preclinical studies, the development of a specific human LRH-1 agonist may be the way forward to test the efficacy of LRH-1 in reducing MASH-related complications in humans.

7 Conclusions and future perspectives

NRs-based pharmacological drugs are currently the most promising candidates to obtain FDA approval for MASH treatment. Owing to their wide coverage of the genomic landscape, NRs regulate several hepatic processes including lipid synthesis, lipolysis, mitochondrial function, as well as inflammatory and fibrotic signaling, all of which are deregulated at different stages of MASLD progression (Table 1). Understanding the contrasting effects of some NRs on hepatic physiology and pathophysiology is crucial, as these effects may be due to the differential expression of NRs within liver cell types together with their interaction with other transcription factors. Furthermore, a limitation of present NR therapeutics is the unwanted and often adverse extrahepatic activation of target NRs. Therefore, the liver-specificity of NR agonism/antagonism is vital to maximize the benefits of NR activation through synthetic ligands and will be a way ahead for more precise and tactical MASH therapies. Further translational evidence should accelerate the entry of more NRs in the trial pipeline, alongside genetic screening for pathogenic NR mutations that may predict MASH development and progression. Additionally, future trials should take into account the differential NR targeting for lean NASH *vs.* diabetes associated MASH. NR crosstalk is another important area that warrants increased attention while designing future NR-based therapeutics for MASLD/MASH. Novel ligands that precisely enhance or reduce NR factor crosstalk are expected to minimize side effects and resistance observed with endogenous NR ligands. Furthermore, unorthodox targeting concepts, such as dual NR ligands, allosteric ligands, and ligands targeting different NR domains or NR-related protein-protein interactions may add refinement to existing NR-based pharmacology for treating MASLD/MASH.

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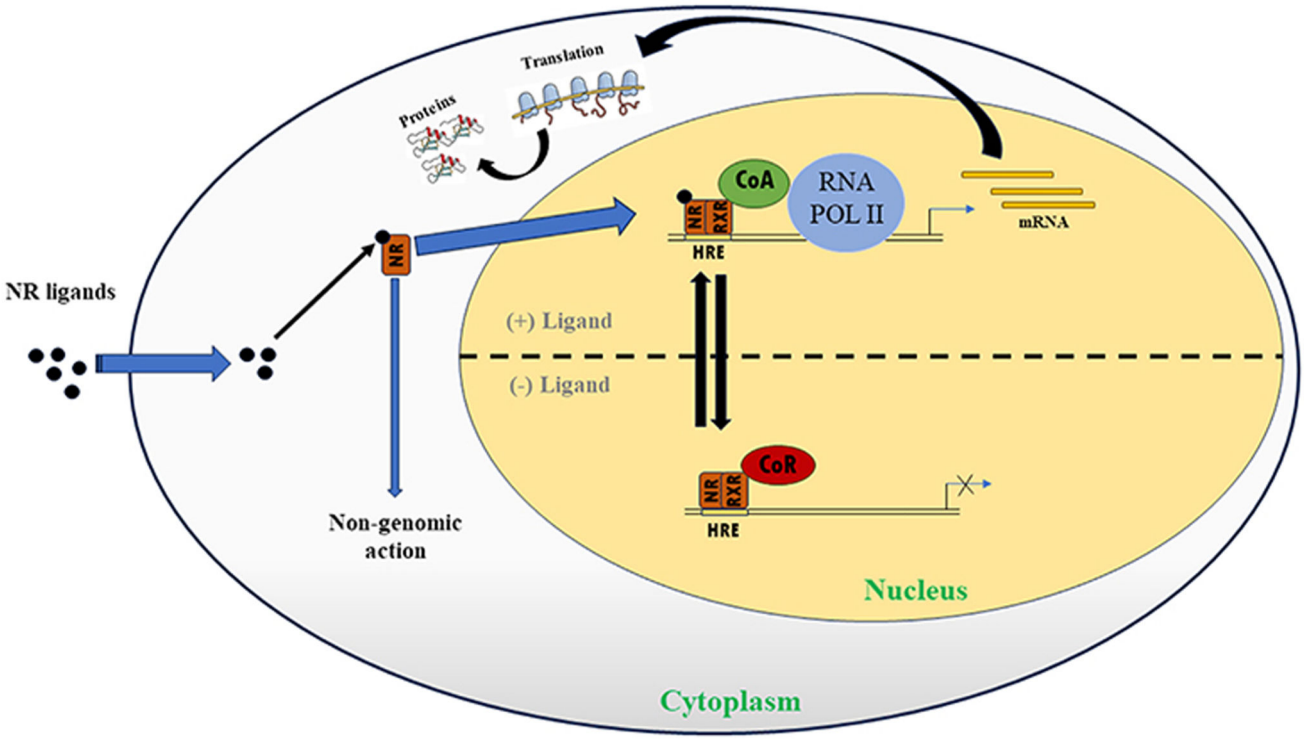

Fig. 1. Molecular mechanisms of NR action.

Nuclear receptor (NR) ligands which may include hormones, lipids, cholesterol derivatives, and xenobiotics may bind to either cytosolic or nuclear resident NRs which results in the binding of NRs to their cognate response elements such as hormone response elements (HREs) on the promoter/enhancer region of the target genes. Upon ligand binding NRs evoke a dynamic exchange of nuclear receptor corepressor (CoR) with nuclear receptor coactivator (CoA) complexes. The CoA has a histone acetylase activity which helps in the opening of the nucleosomes and initiation of RNA polymerase II (POL II) mediated transcription. The mRNA synthesized in response to NR activation further results in protein synthesis and alteration of cellular function. Besides the classical genomic action of NRs, cytosolic NRs may also induce non-genomic signaling via interaction with cytoplasmic proteins.

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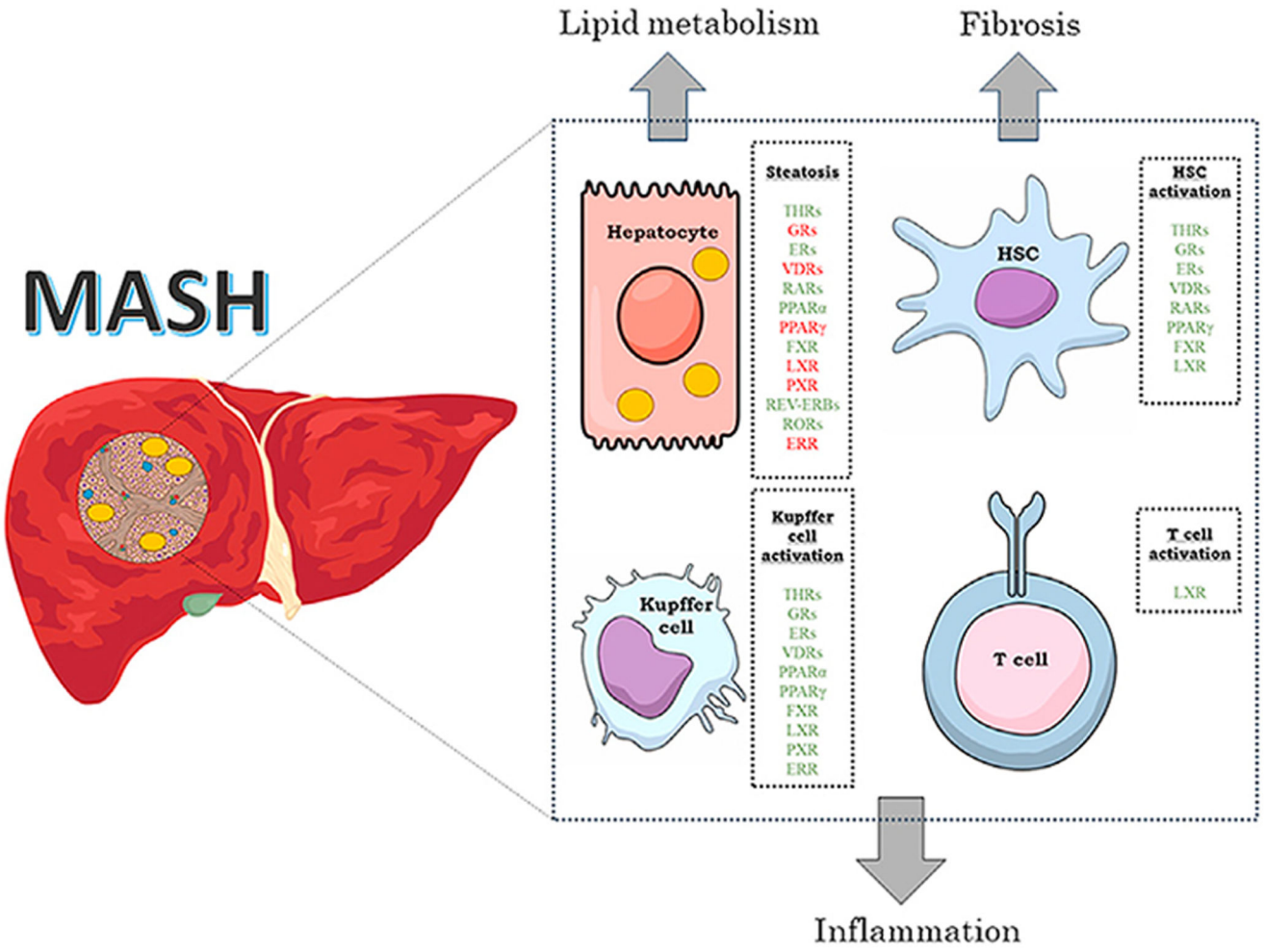

Fig. 2. Cell-specific NRs modulation of metabolism, inflammation, and fibrosis response in MASH.

Multiple nuclear receptors (NRs) as shown in this schematic play both distinct and overlapping cellular roles in regulating diverse aspects of hepatic lipid metabolism, immunomodulation, and fibrosis response during metabolic dysfunction-associated steatohepatitis (MASH) pathogenesis via their distinct action on hepatocytes, immune cells (Kupffer cells & T cells), and hepatic stellate cells (HSCs). The green font color denotes NRs that negatively regulate the pathogenic processes of hepatosteatosis, immune cell activation (inflammation), and HSC activation (fibrosis), and the red font color denotes NRs that positively regulate them. Abbreviations: THRs, thyroid hormone receptors; GRs, glucocorticoid receptors; ERs, estrogen receptors; VDRs, vitamin D receptors; RARs, retinoic acid receptors; PPARα, peroxisome proliferator-activated receptor α; FXR, farnesoid X receptor; LXR, liver X receptor; PXR, pregnane X receptor; RORs, RAR-related orphan receptors; ERR, estrogen-related receptor; RXR, retinoid X receptor.

Table 1
Effects of NRs targeting on liver pathology in MASLD/MASH.

NRs	Agonist or antagonist	Research methods	Key findings	NR activation/inhibition	References
THRs	Agonist (GC-1)	Mouse/rat	Anti-steatosis effects	Activation	25,26
	Thyroxine	Mouse	Anti-steatosis action and anti-inflammatory effects	Activation	27
THRβ	Liver-specific agonist (Resmetirom)	Human	Anti-steatosis, anti-inflammatory, and anti-fibrotic effects	Activation (clinical trial: NCT03900429; active)	37–40
GR	Genetic silencing	Mouse	Anti-steatosis effects	Inhibition (GR KO in hepatocytes)	43
	Genetic silencing	Mouse	Pro-inflammatory effects	Inhibition (GR KO in macrophage)	44
ER	Genetic silencing	Mouse	Pro-steatosis effects	Inhibition (ER KO)	50,54
	ERα and ERβ agonists	Mouse	Anti-inflammatory effects	Activation	55,63
VDR	Agonist (vitamin D3)	Mouse	Anti-steatosis, anti-inflammatory, and anti-fibrotic effects	Activation	67
RARα	Agonist	Mouse	Anti-steatosis effects	Activation	85
RARβ	Agonist	Mouse	Anti-steatosis and anti-fibrotic effects	Activation	87–89
RXR	Agonist	Mouse	Anti-steatosis effects	Activation	93
PPARα	Agonist	Mouse	Anti-steatosis and anti-inflammatory effects	Activation	107
	Pemafibrate	Human	Improvement in liver stiffness and ALT levels	Activation (clinical trial: NCT03350165; completed)	110
PPAR β/δ	Agonist	Mouse	Reduction in liver injury	Activation	115
PPAR γ	Agonist	Mouse	Anti-inflammatory and anti-fibrotic effects	Activation in macrophage and HSCs	121–127
PPARα/γ	Agonist (Saroglitazar)	Human	Anti-steatosis, anti-inflammatory, and anti-fibrotic effects	Activation (clinical trial: EVIDENCES II; completed)	133
FXR	Agonist	Mouse	Anti-steatosis, anti-inflammatory, and anti-fibrotic effects	Activation	136–138
	REGENERATE Obeticholic acid GS-9674	Human	Anti-steatosis, anti-inflammatory, and anti-fibrotic effects	Activation (clinical trial: NCT02548351; completed), (clinical trial: NCT01265498; completed), (clinical trial: NCT02854605; completed)	146–148
LXR	Agonist	Mouse	Pro-steatosis effects	Activation (hepatocytes)	152
	Agonist	Mouse	Anti-inflammatory effects	Activation (macrophage)	154
PXR	Agonist	Mouse	Pro-steatosis effects	Activation	159,160
REV-ERB	Agonist	Mouse	Anti-steatosis, anti-inflammatory, and anti-fibrotic effects	Activation	166–168
RORα	Genetic silencing	Mouse	Pro-steatosis effects	Inhibition (liver-specific ROR KO)	171–174
	Overexpression	Mouse	Anti-inflammatory effects	Activation	175
ERRα	Antagonist	Mouse	Anti-steatosis effects	Inhibition	185
CAR	Agonist	Mouse	Pro-steatosis effects	Activation	186–188
SHP	Overexpression	Mouse	Anti-inflammatory effects	Activation	195
HNF4α	Antagonist	Mouse	Pro-steatotic effects	Inhibition	210

NRs	Agonist or antagonist	Research methods	Key findings	NR activation/inhibition	References
LRH-1	Genetic silencing	Mouse	Pro-steatosis and pro-inflammatory effects	Inhibition (LRH-1 KO)	213

Abbreviations: NRs, nuclear receptors; THR, thyroid hormone receptor; GR, glucocorticoid receptor; ER, estrogen receptor; VDR, vitamin D receptor; RAR, retinoic acid receptors; RXR, retinoid X receptors; PPARα, peroxisome proliferator-activated receptorα; HSCs, hepatic stellate cells; FXR, farnesoid X receptor; ALT, alanine transaminase; LXR, liver X receptors; PXR, pregnane X receptor; ROR, RAR-related orphan receptor; ERR, estrogen-related receptor; CAR, constitutive androstane receptor; SHP, small heterodimer partner; HNF4α, hepatocyte nuclear factor 4α; LRH-1, liver receptor homolog-1.

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