Nuclear receptors and transcriptional regulation in non-alcoholic fatty liver disease

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ABSTRACT

Background: As a result of a sedentary lifestyle and excess food consumption in modern society, non-alcoholic fatty liver disease (NAFLD) characterized by fat accumulation in the liver is becoming a major disease burden. Non-alcoholic steatohepatitis (NASH) is an advanced form of NAFLD characterized by inflammation and fibrosis that can lead to hepatocellular carcinoma and liver failure. Nuclear receptors (NRs) are a family of ligand-regulated transcription factors that closely control multiple aspects of metabolism. Their transcriptional activity is modulated by various ligands, including hormones and lipids. NRs serve as potential pharmacological targets for NAFLD/NASH and other metabolic diseases.

Scope of review: In this review, we provide a comprehensive overview of NRs that have been studied in the context of NAFLD/NASH with a focus on their transcriptional regulation, function in preclinical models, and studies of their clinical utility.

Major conclusions: The transcriptional regulation of NRs is context-dependent. During the dynamic progression of NAFLD/NASH, NRs play diverse roles in multiple organs and different cell types in the liver, which highlights the necessity of targeting NRs in a stage-specific and cell-type-specific manner to enhance the efficacy and safety of treatment methods.

Keywords Non-alcoholic fatty liver disease (NAFLD); Non-alcoholic steatohepatitis (NASH); Nuclear receptors (NRs); Transcriptional regulation

1. INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is increasing in lockstep with the obesity pandemic [1]. NAFLD refers to fat accumulation in the liver and is mostly asymptomatic. However, approximately 20% of NAFLD patients progress to a more advanced stage of NAFLD called non-alcoholic steatohepatitis (NASH) that is characterized by inflammation and fibrosis in addition to fatty liver and often leads to liver dysfunction and liver cancer. Currently, there is no FDA-approved pharmacological therapy for NASH [2].

The nuclear receptor (NR) superfamily has great potential for therapeutic targeting, especially for metabolic diseases [3], and serves as a target for ~16% of approved small molecule drugs [4]. NRs function directly at the genome to control transcription, often in response to small lipophilic ligands. Endogenous ligands include steroid and thyroid hormones, retinoids, and metabolites of vitamins, fatty acids, and cholesterol [5]. Drugs targeting numerous NRs, including farnesoid X receptor (FXR), peroxisome proliferator-activated receptors (PPARs), and thyroid hormone receptor (TR), are currently in clinical trials for treating NASH. However, while this review was being written, one promising candidate, the FXR agonist obeticholic acid, proved to be disappointing in phase III clinical trials as significant fibrosis resolution was not observed [6]. Thus, understanding NRs’ biology at a finer resolution is imperative for enhancing the efficacy and safety of potential NASH treatments.

Humans have 48 NRs as defined by shared structural and functional features, including DNA-binding and ligand-binding domains (DBD and LBD, respectively), which have been comprehensively summarized [3,7]. NRs with known important functions in the liver have been reported to play a role in NAFLD/NASH development. NAFLD/NASH is a multicellular disease during its progression, and NRs regulate a variety of metabolic and inflammatory pathways in different liver cell populations (Figure 1). NRs with particular relevance to NAFLD/NASH are discussed in four groups. The first group comprises classical hormone receptors, including glucocorticoid receptor (GR), estrogen receptor (ER), thyroid hormone receptor (TR), and vitamin D receptor (VDR). The second group consists of peroxisome proliferator-activated receptors (PPARs), liver X receptor (LXR), farnesoid X receptor (FXR), and pregnane X receptor (PXR), which mainly utilize dietary lipids as their ligands. Many of these NRs function as heterodimers with retinoid X receptor (RXR) [5]. The third group contains REV-ERBs and retinoic acid receptor-related orphan receptors (RORs), which were both traditionally categorized as orphan receptors but are now featured with well-studied circadian transcriptional regulation. The fourth group is composed of orphan receptors whose endogenous ligands remain uncertain, including estrogen-related receptor (ERR), constitutive

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androstane receptor (CAR), small heterodimer partner (SHP), and hepatocyte nuclear factor 4 α (HNF4α).

2. CLASSICAL HORMONE RECEPTORS

2.1. Glucocorticoid receptor (GR)

The GR plays essential roles in regulating the transcription of genes related to glucose homeostasis, stress response, and inflammation. GR is activated upon binding of an endogenous glucocorticoid (cortisol in humans) as well as pharmaceutical ligands, which are commonly prescribed as anti-inflammatory drugs. Fatty liver is one of many adverse metabolic effects of chronic glucocorticoid usage [3].

GR has two major isoforms, of which GRα is more thoroughly studied and responsive to glucocorticoids [9]. The canonical view is that GR undergoes conformational changes upon ligand binding that allows for the dimerization and translocation to the nucleus and then binds to a GR-binding site (GBS) to drive gene transcription by recruiting transcriptional coactivators such as the SRC family [10]. GR has also been shown to repress gene expression through different mechanisms such as transrepression or acting through non-canonical GBS [11,12]. In the liver, CCAAT-enhancer-binding protein beta (CEBPβ) maintains chromatin accessibility for GR binding [13]. GR monomers have also been found to co-localize with another NR, HNF4α, on chromatin. Hepatic-specific effects of GR action may involve interactions with physiologically regulated coactivators such as peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α), which is induced by fasting [14]. The fasting state alters the chromatin landscape by exposing enhancer sites and allows crosstalk to occur between GR and cAMP-responsive element-binding protein 1 (CREB1) for increased expression of gluconeogenic genes in a short fasting period or between GR and peroxisome proliferator-activated receptor alpha (PPARα) in expressing ketogenic or fatty acid oxidation genes during prolonged fasting [15].

Glucocorticoid levels have a circadian rhythm [16] and, intriguingly, higher circulating concentrations of glucocorticoids during the night promotes GR binding to distant metabolic enhancers associated with lipid and amino acid metabolism in rodents [17]. The circadian NR, REV-ERBα, has been suggested to maintain temporal glucocorticoid response of genes involved in carbohydrate and lipid metabolism but not inflammation [18].

Mouse models have demonstrated links between GR and NAFLD. Due to the essential role of GR for survival, global knockout mouse models are not viable [19]. Liver-specific GR knockout mice have normal hepatic histology [20], but loss of GR in the livers of genetically obese mice, db/db mice, ameliorates the hepatic steatosis phenotype by derepressing the direct GR target gene, hairy enhancer of split 1 (Hes1) [21] (Table 1). Macrophages have been shown to closely mediate inflammation in NASH [22], and decreased GR expression in Kupffer cells contributes to obesity-induced liver inflammation by lowering the expression of a direct GR target anti-inflammatory effector, glucocorticoid-induced leucine zipper (Tsc22d3) [23]. Comprehensive genome-wide binding studies of macrophage GR revealed a more complex transcriptional regulation mechanism [24].

In NAFLD patients, serum and urinary cortisol levels are elevated [25]. GR expression was shown to negatively correlate with liver steatosis and inflammation but not fibrosis in a cohort of pediatric NAFLD patients [26]. Conversely, glucocorticoid therapy, which is widely used to treat inflammatory disorders, may contribute to NAFLD [27] in part by stimulating lipolysis in adipose tissue [28]. Even with the potential of glucocorticoids in ameliorating inflammation in NASH, given the complex pharmacology, GR is not necessarily an attractive target for NAFLD/NASH treatment.

2.2. Estrogen receptor (ER)

Estrogens are essential for the development and function of the reproductive system, especially in females. The effects of the classic estrogenic hormone estradiol (E2) are mediated by ER [29–31]. There...
Table 1 – Summary of nuclear receptors involved with transcriptional regulation in NAFLD/NASH.

| Nuclear receptor                                    | Alias used in this review | Gene name       | Endogenous ligands                                                                 | Knockout (KO) mouse models                                                                 | NASH therapeutics in clinical trials |
|-----------------------------------------------------|---------------------------|-----------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|-------------------------------------|
| **Classical hormone receptors**                      |                           |                 |                                                                                     |                                                                                           |                                     |
| Glucocorticoid receptor                              | GR                        | NR3C1 (human)   | Cortisol                                                                            | Global KO models are not viable [19].                                                    | None                                |
|                                                      |                           | Nr3C1 (mouse)   |                                                                                     | Liver-specific KO mice have normal hepatic histology [20].                               |                                     |
|                                                      |                           |                 |                                                                                     | Liver-specific KO in db/db mice ameliorates hepatic steatosis phenotype [21].             |                                     |
| Estrogen receptor αδ                                  | ERα                       | ESR1 (human)    | Estradiol                                                                           | Global and liver-specific KO of ERα induces hepatic steatosis [44].                       | None                                |
|                                                      |                           | Erσ1 (mouse)    |                                                                                     |                                                                                           |                                     |
| Thyroid receptor βδ                                   | TRβ                       | THRβ (human)    | Thyroid hormone                                                                     | Expression of a TRβ mutant that is unable to bind to TH led to hepatic steatosis [69].   | None                                |
|                                                      |                           | Thrb (mouse)    |                                                                                     |                                                                                           |                                     |
| Vitamin D receptor                                    | N/A                       | VDR (human)     | 1,25(OH)D3, bile acid                                                              | VDR-deficient mice have various reported hepatic inflammation and fibrosis phenotypes [61–63]. | None                                |
|                                                      |                           | Vdr (mouse)     |                                                                                     |                                                                                           |                                     |
| **Non-steroid hormone receptors**                    |                           |                 |                                                                                     |                                                                                           |                                     |
| Peroxisome proliferator-activated receptor αδ        | PPARα                     | PPARα (human)   | Fatty acid derivatives                                                              | Global KO and liver-specific KO have exacerbated liver steatosis and obesity phenotype induced by HFD or NASH diets [83,86,89]. | Fibrates drugs (clofibrate and fenofibrate [104,105]) PPARα/β agonist (elafibrate [106]) |
|                                                      |                           | Ppara (mouse)   |                                                                                     |                                                                                           |                                     |
| Peroxisome proliferator-activated receptor γδ         | PPARγ                     | PPARγ (human)   | Fatty acid derivatives                                                              | Liver-specific KO protected mice from fatty liver in HFD-induced or obese mouse models [110,111]. | PPARγ agonists (rosiglitazone and pioglitazone [120–124]) PPARα/γ double agonist (saroglitazar [120]) |
|                                                      |                           | Pparg (mouse)   |                                                                                     |                                                                                           |                                     |
| Liver X receptor αδ                                   | LXRα                      | NR1H3 (human)   | Oxidized cholesterol derivatives                                                    | Global and liver-specific KO mice had cholesterol accumulation in the liver when fed a high-cholesterol diet [129,134]. | None                                |
|                                                      |                           | Nr1h3 (mouse)   |                                                                                     |                                                                                           |                                     |
| Farnesoid X receptor                                  | FXR                       | NR1H4 (human)   | Bile acids                                                                          | Global KO led to systemic and hepatic elevation of cholesterol and triglyceride levels [171]. | FXR agonists (obeticholic acid [6,174]) |
|                                                      |                           | Nr1h4 (mouse)   |                                                                                     |                                                                                           |                                     |
| Pregnane X receptor                                   | PXR                       | NR1I2 (human)   | Endobiotics (bile acid, cholesterol and steroid derivatives)                       | PXR deficiency has various reported effects on NAFLD [180–183].                         | None                                |
|                                                      |                           | Nr1i2 (mouse)   |                                                                                     |                                                                                           |                                     |
| **Circadian nuclear receptors**                       |                           |                 |                                                                                     |                                                                                           |                                     |
| REV-ERBα                                             | REV-ERBα                  | NR1D1 (human)   | Heme                                                                                | Global KO led to decreased bile acid synthesis and accumulation of hepatic steatosis [190,205]. | None                                |
|                                                      |                           | Nr1d1 (mouse)   |                                                                                     |                                                                                           |                                     |
| REV-ERBβ                                             | REV-ERBβ                  | NR1D2 (human)   | Heme                                                                                | Global REV-ERBββ KO exacerbated hepatic steatosis phenotype that was present in REV-ERBα null mice [196]. | None                                |
|                                                      |                           | Nr1d2 (mouse)   |                                                                                     | Liver-specific REV-ERBββ KO had increased hepatic triglyceride levels under HFD conditions [207]. |                                     |
| Retinoic acid receptor-related orphan receptor αδ     | RORα                      | RORA (human)    | Cholesterol derivatives                                                             | Global or liver-specific RORα deficiency has various reported effects on NAFLD [218–220]. | None                                |
|                                                      |                           | Rora (mouse)    |                                                                                     |                                                                                           |                                     |
| Retinoic acid receptor-related orphan receptor γδ     | RORγ                      | RORC (human)    | Cholesterol derivatives                                                             | Both global and liver-specific KO models had improved insulin sensitivity and reduced hepatic gluconeogenesis [223]. | None                                |
|                                                      |                           | Rorc (mouse)    |                                                                                     | RORα/RORγ double-KO elevated hepatic triglyceride levels in mice treated with HFD [217].  |                                     |
| **Orphan receptors**                                  |                           |                 |                                                                                     |                                                                                           |                                     |
| Estrogen-related receptor αδ                           | ERRα                      | ESRα (human)    | Endogenous ligand unclear                                                           | Global KO mice were resistant to HFD-induced NAFLD [234].                                | None                                |
|                                                      |                           | Esra (mouse)    |                                                                                     |                                                                                           |                                     |
| Constitutive androstane receptor                      | CAR                       | NR1I3 (human)   | Endogenous ligand unclear                                                           | Global KO mice had reduced serum triglyceride levels on an HFD without increased hepatic triglyceride levels and attenuated NASH diet-induced fibrosis [248]. | None                                |
|                                                      |                           | Nr1i3 (mouse)   |                                                                                     |                                                                                           |                                     |
| Small heterodimer partner                             | SHP                       | NR0B2 (human)   | No confirmed endogenous ligands                                                     | SHP deficiency has various reported effects on NAFLD/NASH [259–262].                     | None                                |
| Hepatocyte nuclear factor 4α                          | HNF4α                     | HNF4A (human)   | Potentially fatty acids                                                             | Global KO leads to early embryonic lethality [281].                                       | None                                |
|                                                      |                           | Hnf4a (mouse)   |                                                                                     | Liver-specific KO has fatty liver, hepatomegaly, and increased plasmid bile acid levels [77,262]. |                                     |

* The selected isoforms of the respective NRs presented in this table are those that are more relevant for NAFLD/NASH.
are two ER isoforms [32], with ERα being the most well-characterized in the liver. Upon binding to an estrogenic ligand, ERs dissociate from cytoplasmic heat shock protein 90 and translocate into the nucleus [33], although recent studies have shown that E2 is not absolutely required for the transcriptional and DNA-binding activity of ERs [34]. ERs recruit coactivators of the p160 (SRC) family to activate target gene transcription. ERα also indirectly binds to DNA in a tethered fashion through other transcription factors such as the Forkhead box (FOX) family and activator protein 1 (AP-1), which can activate or repress transcription activity of target genes [35–37]. The pattern of ER binding to chromatin is tissue-specific. The common ER-binding sites between the liver and other tissues match the canonical estrogen response elements (ERE), and these sites are less accessible prior to E2 treatment. In contrast, liver-specific ER binding is suggested to occur through tethering, and binding is more accessible prior to E2 induction [38,39]. In the liver, the majority of ERα-binding sites are enriched with the transcription factor AP-1, suggesting that the dominant mode of binding in chromatin is cooperative. Genes with enriched ERα-binding sites at promoter regions such as Nr0b2 (SHP) and Stat3 are associated with lipid and glucose metabolism [40]. The beneficial effect of estradiol on the liver, including repressing lipid biosynthesis and gluconeogenesis, can be indirectly mediated by a direct target of ERα, Stat3 [41,42]. The activation of Stat3 has been corroborated in isolated hepatocytes [43]. Multiple genetic mouse models of whole-body or liver-specific ERα knockout have been reported. Loss of ERα induces hepatosteatosis in both male and female mice [44] (Table 1). Liver-protective metabolic effects of estrogen are mediated not only by hepatic ERs, but also through its function in extrahepatic tissues such as promoting fatty acid oxidation and insulin response in skeletal muscle and adipose tissue [45,46]. Interestingly, the estrous cycle has been shown to influence the liver transcriptome in female mice, with the lowest expression of hepatic lipid synthesis genes when estrogen was at the highest level; acute E2 treatment of mice also decreased the expression of these lipid-synthesis genes [47]. In humans, menopausal women are at increased risk of developing NAFLD [48,49]. Estrogen treatment of diabetic patients demonstrated a protective effect on the liver as well as whole-body metabolism [50], but at present, ER is not a widely investigated clinical target for NAFLD/NASH therapies.

2.3. Thyroid hormone receptor (TR)

Thyroid hormones (TH) crucially control growth and metabolism. Triiodothyronine (T3), the major active form of TH, can both upregulate and downregulate genes involved in lipid, carbohydrate, and amino acid metabolism. For example, T3 activates the transcription of fatty acid anabolism genes Fasn and Acaca [51,52] and the lipid catabolism gene znic-a2-glycoprotein [53]. T3 also negatively regulates the transcription of lipogenic genes such as Srebf1 and Vldlr [54,55]. Two major receptors, TRα and TRβ, mediate TH actions [56,57]. TRβ is the predominant isoform in the liver and regulates transcription by binding to TH response elements (TREs) in chromatin, predominantly as heterodimers with RXR [58,59]. Other NRs that heterodimerize with RXR such as LXR [60] and PPARα [61], have been shown to bind to TRE-binding elements, indicating a competition mechanism among these NRs.

In the absence of TH, TR represses basal gene expression by recruiting a corepressor complex containing nuclear receptor corepressor (NCoR) and histone deacetylase 3 (HDAC3) [62,63]. TH binding leads to the dissociation of TR from corepressors while stabilizing the recruitment of coactivators such as the SRC family, which results in chromatin becoming more accessible and increasing gene transcription [64]. This model is likely oversimplified, as recent studies suggested that suppression of some TRβ1 target genes in the hypothalamic liver is NCoR1-independent [55], while others showed that the corepressor can be dismissed without further recruitment of coactivators or remain at functional enhancers while coactivators are recruited [65]. Preclinical studies have demonstrated a protective role for TH in NAFLD [66,67]. Conversely, mice expressing a TRβ1 mutant that cannot bind TH (TβRβV) developed liver steatosis [68] (Table 1). TR agonism targets various steps of lipid metabolism and reduces hepatic steatosis and inflammation in rats and mice [69,70], and there is epidemiological evidence that hypothyroidism is a risk factor for NAFLD [71]. In humans, several thyroid hormone receptor β (TRβ) agonists have demonstrated beneficial effects in clinical trials in reducing serum and liver lipid levels as well as improving liver function in patients with NAFLD/NASH [66,72,73].

2.4. Vitamin D receptor (VDR)

VDR mediates the genomic actions of vitamin D. VDR can either homodimerize or heterodimerize with RXR on DNA [74]. The major active form of vitamin D is 1,25(OH)2D3, and the vitamin ligand converts DNA-bound VDR homodimers into VDR-RXR heterodimers [75], which recruit corepressors or coactivators to regulate gene transcription [76]. While best known for its physiological function in skeletal health [77], vitamin D has more recently been implicated in metabolic syndrome and NAFLD [78]. In rodent models, exposing mice to artificial sunlight or treating them with 1,25(OH)2D3, attenuated high-fat diet (HFD)-induced hepatic steatosis and NASH diet-induced liver inflammation and fibrosis [79,80]. However, there is some controversy regarding the function of VDR. Several groups reported that VDR-deficient mice are resistant to HFD-induced or ob/ob model-induced liver steatosis and inflammation by reducing lipid synthesis and increasing fatty acid oxidation [81–83], while other long-term studies reported that the lack of VDR can exacerbate hepatic inflammation and fibrosis [84,85] (Table 1). Notably, although VDR has minimal expression in normal hepatocytes, it is upregulated in NAFLD [83]. However, non-parenchymal cells in the liver, especially stellate cells, Kupffer cells, and biliary epithelial cells, exhibit abundant expression of VDR [84,85]. The VDR agonist calcitriol or 1,25(OH)2D3 is able to ameliorate TGFβ1-induced stellate cell activation in vitro, and HFD-induced liver steatosis and inflammation in vivo [84,85]. In stellate cells, the proposed mechanism involves genomic antagonism between VDR and TGF-β downstream effector Smad3 [85]. This paradox of physiological effects between VDR and vitamin D can be explained by their distinct functions, including a VDR-independent mechanism in mediating the biological effect of vitamin D and the receptor’s ability to bind to other endogenous ligands such as bile acid [86]. Moreover, the conflicting results of VDR function in NAFLD may be attributed to the diverse roles of VDR at different stages of NAFLD development [83,87]. This notion is supported by upregulated VDR in the liver of NAFLD human patients with simple steatosis but to a lesser extent in individuals with NASH [83], suggesting the necessity of interrogating VDR function with NAFLD progression in a tissue/cell-type specific manner. As the role of VDR is not fully clear, there are currently no clinical trials targeting VDR for treating NAFLD/NASH.

3. NON-STEROID HORMONE RECEPTORS

3.1. Peroxisome proliferator-activated receptors (PPARs)

PPAR, as a key regulator of lipid metabolism, is one of the most thoroughly studied NRs in the context of NAFLD. PPAR has three
isoforms, alpha (α), beta/delta (β/δ), and gamma (γ), which are distributed differently across tissues [88]. PPARα is mainly expressed in the liver and brown adipose tissue. PPARβ/δ is more ubiquitously expressed. PPARγ is predominant in adipose tissue but can be robustly induced in the liver in obese/NAFLD conditions [89,90]. Fatty acid derivatives are the main endogenous ligands of PPARs. PPARβ/δ shares several similar functions to PPARα in terms of promoting fatty acid oxidation and improving NAFLD by functioning in the liver and extrahepatic tissues [91,92]. However, few studies have generated a comprehensive view of transcriptional regulation of PPARβ/δ in the liver. Therefore, we focus mainly on PPARα and PPARγ in this review.

3.1.1. PPARα

PPARα is a nutrient sensor and its expression and activity in the liver can be stimulated by fasting or HFD [93]. The regulation of transcription by PPARα in various contexts has been comprehensively detailed elsewhere [94]. In the liver, PPARα binds to chromatin, often as a heterodimer with RXR, and upon ligand binding, lipid catabolism is largely promoted by activating genes associated with mitochondrial and peroxisomal fatty acid oxidation [95]. PPARα also exerts repression activity on gene transcription, in some cases by PPARα interfering with the recruitment of GR [96], and in others by tethering to other transcription factors [94].

PPARα plays an important role in NAFLD development. In mouse models, HFD elevates hepatic PPARα expression in a circadian rhythmic manner. Interestingly, the lipid-lowering effect of a PPARα agonist is more prominent at the peak expression of PPARα [97]. PPARα null and liver-specific PPARα knockout mice both exacerbated HFD- or NASH diet-induced obesity and liver steatosis [93,98,99] (Table 1). Moreover, PPARα inhibits NASH diet-induced fibrotic and inflammatory gene expression by physically interacting with NF-κB and AP-1 [95,100].

In humans, PPARα expression negatively correlates with NASH severity [101]. Fibrate drugs that mainly activate PPARα such as clofibrate and fenofibrate have been clinically used to treat elevated triglyceride levels [102,103], but their effect on NASH has been disappointing [104,105]. However, a dual PPARα/δ agonist elafibanor showed promise as a NASH therapy in a clinical trial [106].

3.1.2. PPARγ

PPARγ is the master regulator of adipocyte biology [107]. The dominant chromatin-binding mode of PPARγ is to form a heterodimer with RXR and switch from corepressor to coactivator complex recruitment upon ligand activation [108]. It is expressed at very low levels in the liver. However, interestingly, HFD upregulates hepatic PPARγ expression in a circadian rhythmic manner and results in an oscillatory change of target gene expression [97,109]. Hepatocyte-specific deletion of PPARγ protects mice from fatty liver in HFD-induced or obese mouse models [110,111] by reducing the expression of genes associated with lipogenesis and lipid transport (Table 1). Paradoxically, PPARγ agonists, including anti-diabetic thiazolidinedione drugs (TZDs), are able to ameliorate NAFLD in part by redirecting fatty acids and triglycerides to be stored in adipose tissue [112].

PPARγ is also present in Kupffer cells and stellate cells. Indeed, PPARγ agonists reduce the expression of pro-inflammatory genes in Kupffer cells, contributing to the amelioration of inflammation in HFD-induced hepatosteatosis [113]. The anti-inflammatory effect of PPARγ can be explained by its transcriptional activity [114]. Furthermore, the PPARγ cistrome in peritoneal macrophages revealed that macrophage lineage factors SPI1 (PU.1) and CEBPβ co-occupy with PPARγ [115,116], which then enhance permissive chromatin configuration compared to sites with PPARγ binding alone. Ectopic expression of PPARγ in macrophages selectively enhances chromatin accessibility and gene transcription at sites that may be open prior to PPARγ binding but not at sites with repressive histone marks, suggesting a facilitating role of PPARγ in regulating transcription [116]. In stellate cells, PPARγ expression is predominantly in the quiescent state but diminished in the activated state. PPARγ ligand treatment in activated stellate cells or a liver fibrotic mouse model can reduce collagen gene expression both in vitro and in vivo, but the mechanism of how PPARγ functions on chromatin to suppress gene expression is not completely understood [117,118].

In humans, liver PPARγ transcript levels are elevated in patients with NAFLD/NASH [119]. TZDs, including rosiglitazone and pioglitazone, which are widely used to treat diabetes, have been evaluated in several clinical trials and were shown to alleviate steatosis and inflammation, but with minimal reduction of fibrosis [120–124]. A PPARγ dual agonist sarelgitanaz has been approved for NASH treatment in India, and a prospective randomized clinical trial is being conducted (https://clinicaltrials.gov/ct2/show/NCT02265276) [120].

3.2. Liver X receptor (LXR)

LXR plays an essential role in whole-body cholesterol homeostasis. LXR has two isoforms, LXRα and LXRβ. LXRα is highly expressed in the liver, macrophages, and intestine, while LXRβ is more ubiquitously expressed. Oxidized cholesterol derivatives appear to be the main physiological ligands for LXR [125,126]. Earlier studies and the recent genome-wide approach consistently demonstrated that LXR function on chromatin mainly occurs as a heterodimer with RXR [60,125,127]. They are mostly located within open chromatin regions, suggesting that the LXR-RXR heterodimer is a binding pattern that promotes gene transcription. Moreover, LXR agonist treatment can induce a great number of new binding sites, illustrating a dynamic rather than stationary binding of LXR, switching from a corepressor to a coactivator interaction upon ligand treatment [60].

The activation of LXRs stimulates direct cholesterol secretion from the intestine and cholesterol efflux, the process with which cholesterol is delivered to the liver for excretion and subsequently eliminated from the body [128–131]. This protective process mainly occurs through direct LXR transcriptional regulation such as enhancing the expression of the ATP-binding cassette (ABC) transporter family [132,133]. Global and liver-specific deletion of LXRα in mice fed a high-cholesterol diet result in cholesterol accumulation in the liver [129,134] (Table 1). Nonetheless, activation of LXR can also stimulate triglyceride synthesis in the liver by directly and indirectly activating lipogenic genes, exacerbating steatosis and hypertriglyceridemia [135–137].

Another essential role of LXR in NAFLD/NASH is its anti-fibrotic and anti-inflammatory activity [138,139]. Compared to its function in stellate cells, LXR in macrophages/Kupffer cells is more extensively characterized. A Kupffer cell-specific LXRα knockout mouse model revealed that LXRα is required to maintain the identity of Kupffer cells [140]. LXR binding is positively correlated with active histone modifications, and the consumption of a NASH diet largely redistributed LXR-binding sites. A SUMOylation-dependent transrepression model of LXR has been proposed [141,142], although the overall importance of transcriptional repression by LXR is controversial [143]. Conversely, the inhibitory effect of LXRs on inflammatory genes was also shown to be SUMOylation-independent, and more importantly, secondary to the activation of a direct target gene of LXR, Abca1 [144]. Additionally, LXRs can repress a subset of inflammatory genes by directly binding to their enhancer elements and reducing chromatin accessibility [145].
One study observed the expression of LXRα in humans to be positively associated with the severity of NAFLD, including not only steatosis but also inflammation and fibrosis [146]. However, another group found that the expression of LXRα was unchanged in NASH patients [147]. Overall, the stimulation of triglyceride synthesis and hypertriglyceridemia has been a major barrier to the therapeutic potential of LXR due to increased hepatic steatosis when treating with an LXR agonist.

### 3.3. Farnesoid X receptor (FXR)
FXR controls multiple metabolic pathways throughout the body, including the homeostasis of bile acid, lipids/cholesterol, and glucose [148]. FXR is mainly expressed in the liver, intestine, and kidney [149]. Bile acids serve as endogenous ligands that activate FXR transcriptional activity, and upon activation, can reduce its ligand level by suppressing the bile acid synthesis enzyme cholesterol 7a-hydroxylase (Cyp7a1) [150], indicating the negative feedback regulatory role of FXR.

FXR mainly acts as a heterodimer with RXR [151]. FXR cistromes in the liver also corroborated that FXR positively regulates target gene transcription [152–154]. In addition to RXR, liver receptor homolog-1 (LRH-1) was found to co-localize with 20% of FXR-binding sites and augmented FXR transcriptional activation on the genes mostly involved with lipid metabolic processes [153,155].

Several studies have proposed that the direct gene repression by FXR contributes to its anti-inflammatory effect [156]. Notably, the functioning motif contains shared elements with other NRs and is independent of the canonical FXR-binding motif [157–159]. For example, FXR competes with PPARα and recruits corepressors, which can then suppress the expression of autophagy genes such as Map1lc3a (LC3a) [160]. Additionally, the interaction between PPARα and HNF4α is rather complex and occurs in a gene-selective manner [161].

FXR can also indirectly repress gene expression. FXR physically interacts with CREB1 and transrepresses the interaction between CREB1 and CRTC2, which serves as the transcriptional activation complex of autophagy genes [162]. Moreover, FXR transrepresses carbohydrate-response element-binding protein (ChREBP) and HNF4α to inhibit glucose-induced glycolytic gene expression [163]. The anti-inflammatory effect of FXR can also be attributed to the transrepression of NF-κB [164,165]. Another well-recognized indirect FXR gene suppression mechanism is the transcriptional activation of another nuclear receptor, SHP [166–169], which is further elaborated in the SHP section of this review. SHP-mediated FXR function not only substantially mediates the metabolic functions of FXR such as reducing lipogenesis, but also modulates its anti-fibrotic effect [170].

Knocking out FXR in mice leads to systematic-elevated and hepatic-elevated cholesterol and triglyceride levels [171] (Table 1). FXR ligand treatment was found to lower blood glucose and triglyceride levels as well as hepatic lipid accumulation in diabetic mouse models. Moreover, treating mice with an FXR agonist attenuated NASH diet-induced inflammation and fibrosis in the liver [172]. This systematic beneficial effect is primarily mediated by FXR transcriptional regulation in the liver, which impacts various metabolic processes, including glycogen synthesis, gluconeogenesis, lipid synthesis, and the maintenance of lipoprotein levels [154,169,173]. In humans, the expression of FXR was attenuated in NASH patients [147]. The FXR agonist obeticholic acid was approved by the FDA for biliary cholangitis therapy, but the recent outcome of a clinical trial for NASH resolution was disappointing [6,174]. Nevertheless, FXR remains an attractive target for NAFLD/NASH [175,176].

### 3.4. Pregnane X receptor (PXR)

PXR crucially connects environmental chemicals, mainly foods, drugs, and toxicants, with whole-body metabolism. PXR is predominantly expressed in the liver and intestine. It is a xenobiotic sensor as well as the receptor of endobiotics, including bile acid, cholesterol, and steroid derivatives [177]. Multiple steroid hormones and their derivatives have been shown to activate PXR by enhancing the interaction between PXR and transcriptional coactivator SRC-1 [177]. Clinical medications for treating metabolic diseases such as statins and metformin can interfere with PXR activity and sometimes result in unwanted side effects such as an increase in hepatic gluconeogenesis [178].

Similar to many other NRs, PXR binds to DNA as a heterodimer with RXR to exert its direct transcriptional regulation [127]. Genome-wide PXR binding and transcriptional regulation within the livers of mice revealed that approximately 20% of upregulated and downregulated genes after PXR activation contain enhanced PXR binding, suggesting that PXR may also act as a transcriptional repressor. Notably, upregulated PXR target genes are mostly involved in cell proliferation and drug metabolism, whereas downregulated PXR target genes are enriched for amino acid and carbohydrate metabolic pathways [179].

The effect of PXR on hepatic lipid metabolism is still unclear due to conflicting mouse studies, in which loss of PXR can either ameliorate or worsen NAFLD [180–183] (Table 1). The more prevalent opinion is that PXR activation induces hepatosteatosis. PXR directly activates the transcription of lipid uptake genes Cldn6 and lipogenic genes PPARY [184], but regulation of some lipogenic genes appears to be more controversial [183]. Additionally, PXR can repress β oxidation and ketogenesis in the liver by transrepressing Foxa2 [182]. PXR has been reported to function differently in human and mouse hepatocytes with regard to gluconeogenesis. In mice, activating PXR reduces hepatic glucose output, mostly by indirect repression. PXR interacts with FOXO1 and CREB1, preventing transcriptional activation of gluconeogenic genes [185,186]. Furthermore, PXR has been shown to compete with HNF4α for the coactivator PGC-1α and impairs HNF4α-induced gene expression associated with bile acid synthesis and gluconeogenesis [187]. Nonetheless, in some human studies, positive regulation of gluconeogenesis along with distinct mechanisms have been reported and summarized [183]. In NASH patients, PXR expression was reduced [188]. With a controversial role in the liver, PXR is not being targeted in clinical trials for NAFLD/NASH treatment at this time.

### 4. CIRCADIAN NUCLEAR RECEPTORS

#### 4.1. REV-ERBs

As a key component of the negative feedback loop of the circadian clock in mammals, REV-ERBs in the liver crucially synchronize whole-body metabolism with food and other zeitgeber stimuli from the environment [189,190]. The REV-ERB family has two isoforms, REV-ERBα and REV-ERBβ. REV-ERBs are highly expressed in various organs, including the liver, heart, and brain [191–193]. Although REV-ERBs were traditionally considered orphan receptors, here heme has recently been identified as the endogenous ligand of REV-ERBs and enhances transcriptional repression activity [184,195].

Unlike many other NRs, REV-ERBs are a constitutive transcriptional repressor. Importantly, the mRNA, protein, and chromatin binding of REV-ERBs all occur in a circadian rhythmic pattern in the liver [198,199,196]. REV-ERBs can function as a monomer or homodimer [197]. The homodimeric form of REV-ERBs is required for recruiting corepressors such as NCoR/SMRT as well as HDAC3 and exerting...
stronger gene repression activity [190,198,199]. A direct competing model between REV-ERBs and ROR on chromatin binding, especially in regulating liver circadian genes, was revealed in multiple studies [192,200]. Interestingly, in contrast to the competition model, a “facilitated repression” mode was also proposed for the interaction between RORα and REV-ERBα on chromatin in regulating fatty acid and steroid metabolic pathways [201].

The current paradigm of how REV-ERBs transcriptionally regulate liver metabolism and circadian rhythm was previously described [202]. The majority of REV-ERB binding is tissue-specific. The liver-specific binding sites that are mainly associated with metabolism and REV-ERBs bind to chromatin in a tethered mode through several other transcription factors such as HNFs [200,203]. The common sites across different tissues only constitute a small portion of REV-ERB binding, which are mainly enriched with circadian genes such as Arntl (Bmal1) and Atpas2. In contrast to tethered binding onto liver metabolism genes, REV-ERBs directly bind to chromatin to repress the transcription of clock genes. A chromatin-looping mechanism of REV-ERBs has been suggested to influence circadian transcriptional regulation [204].

REV-ERBα null mice exhibit hepatic steatosis and reduced bile acid synthesis [190,205]. The hepatic steatosis phenotype can also be exacerbated by knocking down REV-ERBβ [196]. Moreover, disrupted circadian behavior only becomes more pronounced in the REV-ERBαβ double-knockout model, suggesting a redundant function of REV-ERBα and REV-ERBβ [206]. The hepatic-specific knockout of REV-ERBαβ displayed an increase in hepatic triglyceride levels under HFD conditions, which further strengthens a functioning role of REV-ERBαβ, specifically in hepatocytes [207] (Table 1). Additionally, knocking out REV-ERBs leads to the decreased expression of some genes, suggesting a secondary mechanism of REV-ERBs in repressing another repressor such as E4 promoter-binding protein 4 (NFL3L) [205,208]. Synthetic REV-ERB ligands display beneficial metabolic effects, but their specificity remains controversial [209,210]. Studies of REV-ERBα in NASH patients are limited. One group reported a marginally significant downregulation of REV-ERBαx in pediatric NASH patients [26]. Although a putative REV-ERB agonist is commercially available as a dietary supplement for human consumption, there are no ongoing clinical trials targeting REV-ERB for NASH therapy.

4.2. Retinoic acid receptor-related orphan receptors (RORs)

In contrast to REV-ERBs, ROR is generally considered a transcriptional activator, and RORα and RORγ coordinate the circadian rhythms of lipid metabolism and inflammation in the liver [211]. Different cholesterol derivatives can serve as either agonists or inverse agonists of RORα [212–214]. There are three major members in the ROR family. RORα and RORγ are the predominant RORs expressed in the liver [215]. RORγ has multiple isoforms, including RORγt, whose expression is restricted to inflammatory T cells [216]. Genome-wide cistrome profiling revealed that RORs act predominantly as transcriptional activators and bind to shared motifs with REV-ERBs [217]. RORz binding peaks at the trough of REV-ERB expression. In REV-ERB-deficient and over-expressed mice, RORz binding is enhanced and reduced, respectively, especially at the promoters of circadian clock genes such as Bmal1. Almost half of RORα-binding sites overlap with REV-ERBs, but more importantly, they appear at the opposite time phase, suggesting a highly collaborative regulation of ROR and REV-ERBs on the rhythmic expression of target genes [200]. In mouse studies, the function of RORs during NAFLD progression is not consistently reported, which can be attributed to several factors, including diverse roles of ROR in different organs/cells, circadian rhythmic activity, and several isoforms with redundant and distinct functions. It has been shown that RORγ-deficient staggerer mice developed elevated triglyceride levels in the liver [216]. However, several groups found improved metabolic features in both the plasma and livers of staggerer mice under normal chow diet or HFD [219,220]. Significant elevation of hepatic triglyceride levels was observed in hepatic specific RORz/RORγ double-knockout mice treated with HFD but not in single-knockout mice (Table 1). More importantly, the disrupted rhythmic pattern of lipogenic genes in ROR-deficient mice depended on nutrient status, highlighting the role of ROR in integrating feeding status and liver metabolism [217].

In contrast to the minimal liver phenotype observed in ROR single-knockout mice mentioned above, another group found a prominent metabolic phenotype, including obesity, insulin resistance, and hepatic steatosis [221]. The conflicting results between these two studies might be due to different genetic mouse models. Interestingly, the transcriptional repression activity of RORα has indicated that RORα recruits HDAC3 and antagonizes the transcriptional activation of PPARγ on lipogenic genes [221]. In addition to its role in hepatocytes, RORα in monocytes/macrophages also plays a role in HFD-induced hepatosteatosis and inflammation [222] (Table 1). Mechanistically, RORα directly drove the transcription of Kruppel-like factor 4 (KLF4) to promote the resolution of inflammation. Regarding the function of RORγ, whole-body knockout and hepatocyte conditional deletion mouse lines displayed a beneficial role of RORγ deficiency [223], which abolished the direct transcriptional activation of gluconeogenic genes especially at their peak expression, leading to improved insulin sensitivity and a reduction in hepatic gluconeogenesis. Interestingly, cistrome analyses of RORα and RORγ suggested limited redundancy of RORα and RORγ, which contradicts the findings mentioned above [217] (Table 1).

In NAFLD/NASH patients, the downregulation of RORα and RORγ in the liver was reported [224], but RORγt, the predominant isoform of RORγ in lymphoid cells, was found to be increased in NASH patients [225]. Similar to the puzzling results from mouse genetic studies, both synthetic agonists and inverse agonists demonstrated a protective effect on liver metabolism and inflammation in NAFLD mouse models [222,226,227]. Thus, the clinical application of targeting ROR remains to be determined for NAFLD/NASH pharmacological therapeutics.

5. ORPHAN RECEPTORS

5.1. Estrogen-related receptor (ERR)

The ERR family has been identified to play a role in the regulation of energy homeostasis. Of the three ERR isoforms, ERRα has had multiple studies indicating its role in regulating the transcription of genes related to glucose/lipid handling and mitochondrial oxidative capacity [228,229]. ERRα is almost ubiquitously expressed with tissue-specific responses of mitochondrial biogenesis and activity [230]. There are currently no confirmed endogenous ligands for ERRs. ERRs can bind to DNA as a monomer, homodimer, or heterodimer of two ERR isoforms through the ERR response element (ERRE) [229]. Importantly, the transcriptional activity of ERRα is weak and largely depends on coregulators such as PGC-1α/β and corepressor receptor-interacting protein 140 (Rip140) to drive and repress transcription, respectively [231], which critically determines the diverse roles of ERRα in different tissues. Specifically in the liver, ERRα is mainly assisted by PGC-1α to directly activate the expression of a plethora of mitochondrial genes and therefore enhance mitochondrial activity and
fatty acid oxidation [231,232]. Homeobox protein prospero-related homeobox 1 (Prox1) was proposed to be a possible negative regulator by interfering with the interaction between ERRα and PGC-1α [233]. However, as an exception, ERRα has been reported to interfere with PGC-1α recruitment and suppress the expression of the gluconeogenesis gene Pck1 in hepatocytes [232]. The function of ERRα in the liver has been reviewed in detail [231], and the role of ERRα in NAFLD has been identified to be context-dependent and involved with multiple tissues [234]. Loss of ERRα seems to have a protective effect as ERRα null mice are resistant to HFD-induced NAFLD due to reduced expression of direct targets such as Fasn, which is involved in de novo lipogenesis [234,235]. However, ERRα is also shown to be required for post-prandial alleviation of fasting-induced hepatic steatosis mediated by the liver-adipose crossstalk [234] (Table 1). Therefore, a liver-specific knockout of ERRα would be informative to further determine the function of ERRα specifically in the liver. Several synthetic ERRα inverse agonists have been developed and some were shown to improve whole-body metabolism in diet-induced obese animal models [236], suggesting that it would be worthwhile to further investigate the link between ERRα and NAFLD. ERRα studies in human NAFLD patients are limited. A pediatric cohort revealed a minimal association between ERRα expression and NAFLD severity [26]. There are no current ongoing clinical trials targeting ERRα to treat NAFLD/NASH.

5.2. Constitutive androstane receptor (CAR)

Originally identified as a player in drug metabolism and detoxification, CAR has recently been recognized to be associated with energy metabolism [237–240]. CAR is abundantly expressed in the liver. Although there are currently no confirmed endogenous ligands, exogenous ligands have been identified such as the anti-epileptic drug phenobarbital (PB) and the synthetic agonist TOPOBOP, which is commonly used in basic research to activate CAR [241]. CAR is a constitutive transcriptional activator [242]. Upon activation, CAR translocates from the cytoplasm to the nucleus and heterodimerizes with RXR mainly through phenobarbital-responsive enhancer modules (PBREM) to drive the transcription of xenobiotic-metabolizing enzymes such as the CYP family [239,243]. As the role of CAR expanded to include the regulation of hepatic energy metabolism, its interaction with different metabolic regulators has been of interest since CAR shares similar binding sites with other NRs. CAR decreases the hepatic transcriptional activity of HNF4α by competing for coactivators, which likely contributes to the down-regulation of hepatic lipid and glucose metabolism [244]. The interaction of CAR with other NRs in regulating liver energy metabolism was systematically investigated. A promoter competition model was proposed in which CAR shifts the transcription of energy metabolic genes that were originally regulated by other NRs through diverting the enhancers to different promoters [245].

The role of CAR in NAFLD pathogenesis remains controversial. Treating genetically obese mice with a CAR agonist improved glucose tolerance, insulin resistance, and reduced lipid accumulation in the liver [246]. However, CAR null mice were reported to normalize the elevated HFD-induced serum triglyceride levels in wild-type mice without increasing hepatic triglyceride levels [247]. Moreover, CAR deficiency was suggested to attenuate fibrosis induced by a NASH-promoting diet [248] (Table 1). In pediatric NAFLD patients, CAR expression was negatively associated with fibrosis but not with steatosis [26]. Thus, the relationship between CAR and NAFLD/NASH should be further assessed, and there are currently no therapies targeting CAR in clinical trials.

5.3. Small heterodimer partner (SHP)

SHP is an atypical NR that lacks a DNA-binding domain and has been found to be predominantly expressed in the liver [166,249]. A small molecule for treating leukemias was shown to bind to SHP, but no endogenous ligands have been identified [250]. SHP often inhibits transactivation driven by other NRs, likely in two steps [251–253]. First, SHP utilizes LXXLL motifs to bind to the ligand-dependent activation function domain (AF2) within target NRs such as GR and ER. The LXXLL–AF2 interaction mode is shared with many coactivators, and thus SHP competes with coactivators for binding to other NRs [252]. In addition, an inherent repression domain or the recruitment of corepressors has been suggested to be required for SHP to exert full repression activity [254–258].

Current studies regarding the role of SHP in NAFLD are not completely understood, which may be due to the divergent function of SHP with NAFLD progression [259]. Overexpressing SHP in the liver was found to increase hepatic triglyceride levels partially through the direct repression of FXR transcription [260]. Likewise, SHP−/− was shown to ameliorate hepatic steatosis in obese leptin-deficient mice [261]. However, another study indicated that the hepatocyte-specific deletion of SHP resulted in inflammation and fibrosis [259]. Consistently, hepatocyte-specific SHP overexpression attenuated NASH diet-induced inflammation and fibrosis by transrepressing NF-κB without affecting steatosis [259,262] (Table 1). In human patients, several studies showed a more pronounced reduction in SHP levels in advanced stages compared to mild NAFLD [262–264], suggesting a stage-specific function of SHP during NAFLD development. Since the function of SHP in NAFLD development remains unclear, no clinical trials are being conducted at this time.

5.4. Hepatocyte nuclear factor 4α (HNF4α)

HNF4α is a master regulator in hepatocyte differentiation and liver function [265,266]. It is abundantly expressed in the liver, pancreas, and several other tissues [267,268]. Fatty acids and several compounds such as acyl-CoA thioesters have been proposed to be endogenous HNF4α ligands [269,270]. HNF4α is generally considered a transcriptional activator [271] and can act as a homodimer or isoform heterodimer [272,273] that regulate different gene expression subsets [273]. HNF4α is known to directly drive 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 such as Cyp7a1, Aebp5, Apoa4, and Pparα [273–280]. Moreover, HNF4α has been shown to interact with other NRs on chromatin to regulate gene transcription, which also contributes to multiple fundamental processes including glycolysis, gluconeogenesis, hepatic lipid metabolism, and cholesterol homeostasis [161,163,187,244].

Given its crucial role in development, global knockout of HNF4α leads to early embryonic lethality in mice [281]. Liver-specific HNF4α knockout mice were found to have a fatty liver phenotype and hepatic steatosis as well as increased bile acid levels in plasma compared to controls [276,282] (Table 1). Furthermore, overexpressing HNF4α in the liver reduces hepatic triglycerides and plasma cholesterol [12]. Synthetic HNF4α antagonists have been discovered and result in hepatic steatosis when administrated in vivo [270]. NASH patients have been demonstrated to have decreased expression levels of HNF4α in the liver attributed to an increased amount of mir-34a, impacting lipid and lipoprotein metabolism [283]. Moreover, the reduction in HNF4α has been shown to play a potential role in the pathogenesis of NAFLD as its direct downstream target and regulator
of triglyceride homeostasis, carboxylesterase 2 (CES2), was identified to be downregulated in NASH patients [284]. Since the dysregulation of HNF4α is associated with NASH/NAFLD along with its significant regulatory role in the liver, examining the potential of HNF4α as a therapeutic would be worthwhile.

6. CONCLUSIONS AND PERSPECTIVES

In this review, we summarized the potential roles of NRs in the development and prospective treatment of NAFLD. The diverse actions of NRs often occur simultaneously in multiple organs and affect the metabolic crosstalk with multiple layers of complexity, highlighting the importance of dissecting the tissue-specific role of NRs for more precise pharmacological treatments. Moreover, NAFLD development is a dynamic process with distinct features that involve various cell types in the liver, which suggests that the targeting strategies for NRs should include not only reversing metabolic disturbances in hepatocytes, but also combating the excessive inflammation/fibrosis in non-parenchymal cells associated with NAFLD progression. Indeed, effective therapies may need to independently target lipid accumulation and hepatic inflammation. Further, in addition to NR ligand-based therapies, it may be desirable to target post-translational modifications such as acetylation of NRs and coregulators [285], which can specifically determine the transcriptional activity of NRs in response to environmental stimuli. Given the heterogeneity of the large population at risk, personalized treatment based on genetic background should also be considered in the future [286–288].

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CONFLICT OF INTEREST

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