Nuclear Receptors as Therapeutic Targets in Liver Disease: Are We There Yet?

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Abstract

Nuclear receptors (NR) are ligand-modulated transcription factors that play diverse roles in cell differentiation, development, proliferation, and metabolism and are associated with numerous liver pathologies such as cancer, steatosis, inflammation, fibrosis, cholestasis, and xenobiotic/drug-induced liver injury. The network of target proteins associated with NRs is extremely complex, comprising coregulators, small noncoding microRNAs, and long noncoding RNAs. The importance of NRs as targets of liver disease is exemplified by the number of NR ligands that are currently used in the clinics or in clinical trials with promising results. Understanding the regulation by NR during pathophysiological conditions, and identifying ligands for orphan NR, points to a potential therapeutic approach for patients with liver diseases. An overview of complex NR metabolic networks and their pharmacological implications in liver disease is presented here.

INTRODUCTION

The nuclear receptor (NR) superfamily is the largest group of transcriptional regulators and consists of 48 members in humans and 49 in mouse. The ligands for NRs include both endogenous and exogenous molecules such as hormones, fatty acids (FAs), bile acids (BAs), drugs, toxins, and intermediary molecules in metabolism (1). Thus, these NRs function to sample the intracellular milieu of hepatocytes for molecules to elicit a response. Agonist binding to NR causes conformational change in the ligand-binding domain (LBD) coordinated with dissociation of corepressors and/or association of coactivators, ultimately leading to activation of gene transcription. These events contribute to regulation of signal transduction pathways under both physiological and pathological conditions (2). Thus, NRs are regarded as promising therapeutic targets for the development of new drugs against a variety of metabolic diseases.

Classic steroid hormone receptors include estrogen and androgen receptors, and are the first identified and cloned NR family members (3). Members of the endocrine receptor class include androgen receptor (AR), estrogen receptor (ER), glucocorticoid receptor (GR), mineralocorticoid receptor (MR), progesterone receptor (PR), retinoic acid receptor (RARα/β/γ), thyroid receptor (TR), and vitamin D receptor (VDR). Hormonal ligands for these receptors have been used therapeutically in daily clinical practice. Numerous other NRs have been cloned, but their natural ligands and functions were initially unknown. These NRs are termed adopted orphan receptors. Their natural ligands and ligand-dependent regulation have been extensively studied and identified to regulate lipid and glucose metabolism, BA homeostasis, drug disposition, reproduction, inflammation, cell differentiation, various aspects of tissue repair including liver regeneration, fibrosis, and finally tumor formation (4). Members of the adopted orphan receptor class include farnesoid X receptor (FXR), liver X receptor (LXR), pregnane X receptor (PXR), peroxisome proliferator-activated receptor (PPAR α/γ/δ), and retinoid X receptor (RXRα/β/γ). Another class of NRs, called enigmatic orphan receptors, has ligands that have been identified, but ligand-dependent regulation has not been firmly established. This class includes receptors such as constitutive androstane receptor (CAR), estrogen-related receptor (ERRα/β/γ), hepatocyte nuclear factor (HNFα/γ), liver-related homolog-1 (LRH-1), and RAR-related orphan receptors (RORα/β/γ). The last class of NRs comprises the true orphan receptors, for which no ligands are known, and in many cases, they even lack the LBD. Some of the members that make up this class include small heterodimer partner (SHP), tailless homolog (TLX), testicular orphan receptor (TR2/4), and germ cell nuclear factor I (GCNF) (5, 6).

NRs provide a framework for a better understanding of liver physiology and pathobiology and for developing novel therapies to treat several liver diseases. Most of the NR family members have multidomain structure with distinct regions engaged in DNA binding, ligand binding, and transactivation. A common structure of NRs consists of an NH_3 terminal ligand-independent activation domain, called AF-1, a central DNA binding domain, a hinge region, and a C-terminal LBD. While AF-1 interacts with cofactors, LBD is unique to NR and allows distinct ligand binding, receptor dimerization, and coregulator interactions (5, 7). For instance, FXR is thought to be bound in an unliganded state to target promoter elements either as a monomer or as a heterodimer with RXRα. Ligand binding results in dissociation of cobound corepressors and recruitment of coactivator proteins, which thus promotes target gene expression.

Coregulators, including coactivators or corepressors, contribute significantly to the complex transcriptional machinery, and add an additional layer of complexity to it. There are approximately 300 coregulators identified so far (5). Binding of an agonist to the LBD results in a conformational change and activation of the NR. Subsequently, a quiescent transcription complex (bound by a corepressor) becomes active by means of unloading corepressors and recruiting coactivators. After

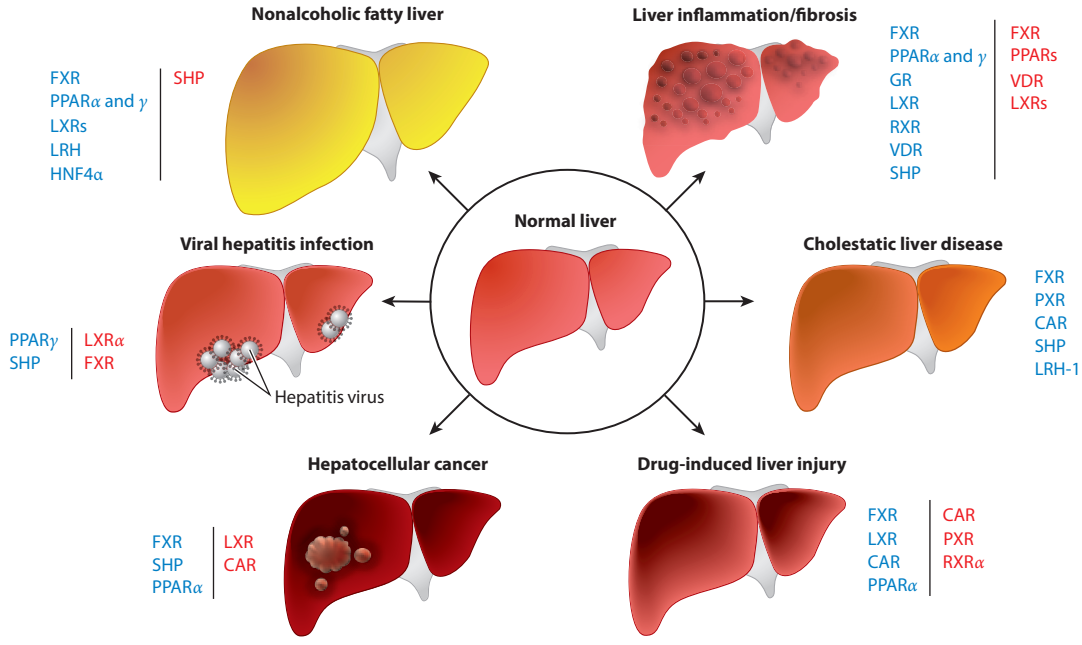

Figure 1

Major kinds of liver diseases discussed in this review: nonalcoholic fatty liver disease, liver inflammation and fibrosis, viral hepatitis infections, cholestatic liver disease, hepatocellular cancer, and drug-induced liver injury. Nuclear receptors are grouped separately based on their regulatory role in diseases: those for which activation alleviates disease (*blue*) and those for which activation exacerbates disease (*red*). Abbreviations: CAR, constitutive androstane receptor; FXR, farnesoid X receptor; GR, glucocorticoid receptor; HNF4α, hepatocyte nuclear factor-4-alpha; LRH, liver-related homolog; LXR, liver X receptor; PPAR, peroxisomal proliferate activating receptor; PXR, pregnane X receptor; RXR, retinoid X receptor; SHP, small heterodimer partner; VDR, vitamin D receptor.

this coregulator exchange, more components of the transcriptional complex join, including RNA polymerase II, which leads to messenger RNA transcription (1). In addition, posttranslational modifications of transcribed protein regulate signal transduction and activation of signaling pathways. This flexibility is key to the adaptation of liver function to various physiological changes and/or stressors, including diets and exposure to drugs, which dictate responses to liver injury and regeneration. Understanding the network of target proteins associated with NRs and their contributions to the development of diseases will advance the development and expand the utilization of NR-targeted small molecules to cure human diseases. NRs have been an established therapeutic target class with many prescribed drugs already on the market. Thus, the focus of this review is to provide an overview of the NR role in liver injury and disease (**Figure 1**) and also to provide an update on therapeutic options (**Table 1**) that target NRs.

ROLE OF NUCLEAR RECEPTORS IN HEPATIC LIPID/GLUCOSE METABOLISM

As the main detoxifying organ of the body, the liver is inherently exposed to high concentrations of absorbed nutrients as well as xenobiotics before delivery to the systemic circulation. The liver also plays a central role in metabolic homeostasis and is a major site for synthesis, metabolism, storage, and redistribution of carbohydrates, proteins, and lipids. NRs play an important role in

Table 1 Selected nuclear receptors as drug targets in liver injury/disease

Target	Drug/compound	Function/pharmacological implication	Model	Reference(s)[a]
Hepatic steatosis				
FXR	GW4064 (agonist)	Prevents diet-induced hepatic steatosis and insulin resistance	In vivo	26
	Px-102/Px-104 (agonist)	Functions similar to GW4064	Phase II clinical trial	27; NCT01999101
LXR	Sulforaphane and resveratrol (antagonist/modulator)	Inhibit lipogenesis in the liver	In vivo	28, 29
PPAR	Rosiglitazone (PPARγ agonist) and fenofibrate (PPARα agonist)	Reduce steatosis with a combination treatment	In vivo, clinical trial terminated	33; NCT00252499
	Pioglitazone (PPARγ agonist)	Reduces steatosis	Phase II clinical trial	34; NCT00633282
	Lobeglitazone (PPARγ agonist)	Improves glycemic and lipid control compared with rosiglitazone and pioglitazone	Phase IV clinical trial	35; NCT02285205
Hepatic inflammation and fibrosis				
FXR	WAY-362450 (agonist)	Protects against NASH by reducing inflammatory cell infiltration	In vivo	56
	OCA (agonist)	Decreases markers of inflammation and fibrosis	In vivo and Phase II clinical trial completed	57, 58; NCT01265498
LXR	GW3965 (agonist)	Suppresses markers of fibrosis and stellate cell activation in primary mouse stellate cells	In vitro	55
PPAR	Hydroxysafflor yellow A (PPARγ agonist)	Inhibits CCl_4- and HFD-mediated liver fibrosis	In vivo	61
	Bezafibrate (PPARα agonist)	Has anticholestatic efficacy in early-stage PBC patients	Clinical trial	64
	Telmisartan (PPARγ agonist)	Alleviates liver fibrosis induced by *Schistosoma mansoni*	In vivo	62
	Curcumin (PPARγ agonist)	Inhibits portal myofibroblast proliferation	In vivo	63
	Pioglitazone and rosiglitazone (PPARγ agonist)	Inhibit collagen synthesis and HSCs activation	In vivo and in vitro, Phase II clinical trial	65; NCT00013598, NCT00062764
	GFT505 (PPAR α/δ agonist)	Alleviates lipid and glucose disorders in NASH	Phase IIb clinical trial	66; NCT01694849
Viral hepatitis infections				
PPAR	Rosiglitazone (PPARγ agonist)	Inhibits HBV replication and hepatitis B surface antigen expression	In vitro	78
	Bezafibrate (PPARα agonist)	Reduces the serum HCV-RNA titer and maintains biliary enzymes level	Observational study in patients	80

(*Continued*)

Table 1 (*Continued*)

Target	Drug/compound	Function/pharmacological implication	Model	Reference(s)[a]
Cholestatic liver disease				
FXR	OCA (agonist)	Reduces GGT, ALP, and ALT levels in patients with primary biliary cirrhosis	Phase IIb clinical trial	59; NCT02308111
	INT-767 (FXR and TGR5 agonist)	Improves liver injury in a mouse model of chronic cholangiopathy	In vivo	95
PXR	Atorvastatin and pregnenolone-16α-carbonitrile (agonist)	Decrease bile acid load in mouse liver by decreasing synthesis and increasing clearance	In vivo	96
CAR	Yin Zhi Huang (modulator)	Accelerates bilirubin clearance in vivo	In vivo and in vitro	98
	CITCO (modulator)	Protects against cholestasis	In vitro	99
	Phenobarbital and 1,4-bis-[2-(3,5-dichlorpyridyloxy)]benzene (agonist)	Reduce serum bilirubin and bile acid levels in BDL mice	In vivo	96
Liver regeneration and hepatocellular carcinoma				
PPAR	Bezafibrate (PPARα agonist)	Inhibits SPT level, which is important for initiation of liver regeneration after partial hepatectomy	In vivo	122
	Thiazolidinediones (pioglitazone and rosiglitazone) (PPARγ agonist)	Decrease the risk of liver cancer in patients with type 2 diabetes	Case-control study	123, 124
Drug-induced liver disease				
FXR	GW4064 (agonist)	Protects against cisplatin-induced toxicity and APAP-induced toxicity	In vivo	119, 130
CAR	TCPOBOP (agonist)	Increases drug resistance in mouse livers and attenuates Fas-induced murine liver injury	In vivo	133, 134
PXR	FLB-12 (antagonist)	Attenuates PXR-mediated APAP hepatotoxicity	In vivo	135
LXR	TO1317 (agonist)	Confers resistance to APAP hepatotoxicity	In vivo	131
PPAR	Clofibrate (PPARα agonist)	Confers protection against APAP-induced toxicity in liver	In vivo	136

[a]The numbers beginning with NCT are ClinicalTrials.gov identifiers for the respective clinical trial.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; APAP, acetaminophen; BDL, bile duct ligation; CAR, constitutive androstane receptor; CCl_4, carbon tetrachloride; CITCO, 6-(4-chlorophenyl) imidazo[2,1-b][1,3]thiazole-5-carbaldehyde-*O*-(3,4-dichlorobenzyl) oxime; FXR, farnesoid X receptor; GGT, γ-glutamyl transpeptidase; HBV, hepatitis B virus; HCV, hepatitis C virus; HFD, high-fat diet; HSC, hepatic stellate cells; LXR, liver X receptor; NASH, nonalcoholic steatohepatitis; OCA/6E-CDCA, obeticholic acid (OCA)[6-ethyl-chedeoxycholic acid (6E-CDCA)]; PBC, primary biliary cirrhosis; PPAR α/γ/δ, peroxisome proliferator-activated receptor α/γ/δ; PXR, pregnane X receptor; SPT, serine palmitoyltransferase; TCPOBOP, 1,4-bis[2-(3,5-dichloropyridyloxy)] benzene; TGR5 (GPR131), G protein–coupled receptor 131.

coordinating several aspects of hepatic lipid and lipoprotein metabolism that may be pertinent not only for understanding the pathogenesis of many diseases, including nonalcoholic fatty liver disease (NAFLD), but also for developing therapeutics.

NRs regulate hepatic cholesterol and lipid homeostasis through a tightly controlled complex network of transcriptional programs. Lipoproteins synthesized by the liver transport endogenous triglycerides (TGs) and cholesterol. Lipoproteins circulate through the blood continuously until peripheral tissues take up the TGs they contain or the liver clears the lipoproteins themselves. Both hepatic production and clearance of TGs from plasma are mediated by a lipoprotein lipase (LPL). Factors that stimulate hepatic lipoprotein synthesis generally lead to elevated plasma cholesterol and TG levels.

In mammals, FA synthesis is catalyzed by acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS)—enzymes that are complexly regulated by various NRs such as PPARα, PPARγ, LXR, and the BA receptor/FXR (8–10). Whereas LXR, FXR, and PPARγ activation increases TG levels by way of upregulation of the lipogenic master regulator sterol regulatory element–binding protein 1c (SREBP-1c), which in turn induces the expression of enzymes involved in de novo lipogenesis (11, 12), PPARα regulates lipogenesis through expression of fatty acid transport protein (FATP), particularly FATP2 and FATP5 in the hepatocytes (12–14). Conversely, PPARα is also involved in the FA oxidation and formation of ketone bodies via transcriptional regulation of mitochondrial 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) synthase (12). SREBP-1c is also a target of SHP in the liver. SHP indirectly modulates SREBP-1c expression/activity by altering cellular cholesterol content. Furthermore, FXR-induced SHP inhibits LXR/LRH-1-mediated transactivation of SREBP-1c and carbohydrate response element–binding protein (ChREBP) expression and de novo lipogenesis (ACC and FAS). The latter results in activation of LPL, which is responsible for clearance of lipids from plasma. Moreover, SHP targets LRH-1- and hepatic nuclear factor-4-alpha (HNF4α)-mediated transactivation of microsomal triglyceride transfer protein (MTP) expression, which is required for TG assembly with apoB as very low-density lipoprotein (VLDL) TGs (15, 16).

The maintenance of glucose homeostasis involves regulation via hormones and NRs that balance both glucose production and/or storage in the liver and glucose uptake in the peripheral tissues. Blood glucose enters hepatocytes via a membrane-bound transporter called the glucose transporter type 2 (GLUT2). GLUT2 possess high capacity but low affinity for glucose (17). In the hepatocytes, glucose is phosphorylated by liver glucokinase (L-GCK), which is a rate-limiting enzyme for hepatic glucose utilization (18). L-GCK, in its inactive state, is bound to glucokinase regulatory protein (GCKR) within the nucleus. An increase in circulating blood glucose (postprandial) and insulin action synergistically causes dissociation of L-GCK from GCKR, as well as translocation to the cytoplasm.

Hepatic glucose metabolism also provides metabolites that activate the transcription factor ChREBP. Recently, LRH-1 has emerged as an upstream regulator of the central GCK-ChREBP axis, with a critical role in the integration of hepatic intermediary metabolism in response to glucose (19). L-GCK is transcriptionally regulated by SREBP-1c, HNF4α, hepatic nuclear factor 6 (HNF6), forkhead box protein O1 (FOXO1), and upstream stimulatory factor 1 (USF1) (12). Gluconeogenesis is regulated by transcriptional activation of phosphoenolpyruvate carboxykinase (PEPCK), fructose-1,6-bisphosphatase, and glucose-6-phosphatase (G6Pase). These enzymes are in turn regulated by many NRs, including FXR, peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC1α), glucocorticoids, and glucagon. It is interesting to note that SHP functions as a negative regulator of energy production in brown adipose tissue by PGC1α inhibition, which demonstrates the complexity in regulation (20).

FOXO1 is a transcriptional activator of PEPCK and G6Pase. Insulin represses PEPCK via Akt-mediated FOXO1 phosphorylation, whereas FXR-induced PPARα activation results in enhanced hepatic PEPCK expression (21). FOXO1 is directly and indirectly activated by PGC1α, HNF4α, ChREBP, and PPARα, and furthermore, PGC1α-FOXO1 complex is considered a potential target for antigluconeogenic therapies for diabetes mellitus (12, 22). SHP plays a key role in both glycolysis and gluconeogenesis in glucose metabolism. For instance, SHP decreases the glycolysis enzyme L-GCK gene expression by inhibiting the transcription of LXRα and PPARγ by directly interacting with their common heterodimer partner RXRα (23). SHP also represses PGC1α-mediated (24) and CCAAT/enhancer binding protein (C/EBP) α (CEBPα)-mediated (25) expression of PEPCK, which results in the inhibition of PEPCK gene transcription.

Nuclear Receptors as Therapeutic Targets in Nonalcoholic Fatty Liver Disease

Farnesoid X Receptor. Currently, there are more than 300 trials listed under NAFLD on ClinicalTrials.gov, some of which are therapeutic trials, with many dietary interventions and toxicity of over-the-counter drugs in NAFLD patient trials included, as well. BA-activated FXR and signal transduction pathways are involved in the regulation of hepatic gluconeogenesis, glycogen synthesis, and insulin sensitivity. Several research groups have examined the effects of FXR deficiency and/or activation in mouse models. Activation of FXR by GW4064 suppressed weight gain in C57BL/6 mice fed with either high-fat diet (HFD) or high-fat and high-cholesterol diet. Treatment of mice with GW4064 also significantly repressed diet-induced hepatic steatosis evidenced by lower TG and free FA level in the liver (26). GW4064 was patented in 1998 and published in 2000. Since then, many pharmaceutical companies have taken GW4064 as a structural template for their efforts to identify novel patentable FXR agonists with the GW-derived trisubstituted isoxazole general structure. However, so far, only one compound out of these different series has made it into the early stages of clinical development: The Px-102/Px-104 from Phenex is currently being tested in a Phase IIa study in patients with NAFLD (27).

Liver X Receptor. LXR agonist T0901317 induces lipogenesis in hepatocytes (28). Treatment of mice with sulforaphane (an Nrf2 activator) suppressed T0901317-induced lipogenesis in mice (28, 29). Interestingly, LXR agonist T0901317 protects mice from HFD-induced obesity and insulin resistance (30). Reasons for this discrepancy in response are not clear, and understanding the mechanism could show LXR as a potential target for prevention of obesity and obesity-associated insulin resistance.

Peroxisome Proliferator-Activated Receptors. PPAR agonists such as fenofibrate, bezafibrate, troglitazone, rosiglitazone, muraglitazar, and tesaglitazar reduce steatosis in oleic acid–induced steatotic HepaRG cells (31). The greatest effects on reduction of steatosis were evidenced with the dual PPARα/γ agonist muraglitazar (31). Farnesol, an activator of both PPARα and FXR, improves metabolic abnormalities in mice (32). Dual PPARα/γ agonists are considered to be effective in the treatment of NAFLD. For instance, rosiglitazone, a PPARγ agonist, in combination with fenofibrate, a PPARα agonist, was in clinical trial, but owing to the small number of participants, the clinical trial was terminated (33). Currently, among many thiazolidinediones, pioglitazone is the only drug that is considered to be an effective therapeutic agent for improving NAFLD (34). Pioglitazone, in combination with Berberine (a plant alkaloid that lowers cholesterol), is in Phase II clinical trial. Lobeglitazone is also a PPARγ agonist, but is highly selective in action. In vivo, lobeglitazone has demonstrated greater effectiveness than

rosiglitazone and pioglitazone in glycemic and lipid control (35). It is in a Phase IV clinical trial to evaluate the efficacy and safety of lobeglitazone once daily for 24 weeks on intrahepatic fat contents in type 2 diabetic (T2D) patients with NAFLD.

Small Heterodimer Partner. SHP is downregulated by several steatotic drugs such as valproate, doxycycline, tetracycline, and cyclosporin A, and also in advanced NAFLD (36), thus favoring the progression and severity of NAFLD (37). However, SHP-null were resistant to HFD-induced fatty liver and obesity (15, 20, 38), which is mediated by the liver Clock and Npas2 genes (39, 40). Interestingly, alcohol-induced macrovesicular lipid vacuoles were diminished in SHP-null mice that were associated with the decreased hyperhomocysteinemia (41). Finally, human fibroblast growth factor 19 (FGF19) is an enterohepatic hormone that is involved in the regulation of hepatic metabolism of BAs, lipids, and glucose. FXR-null mice exhibit steatosis-like symptoms, showing higher hepatic lipid levels than the wild-type mice. FGF19 treatment in FXR-null decreases the hepatic free FA levels and ameliorates disrupted hepatic lipogenesis, which suggests a potential option for the treatment of NAFLD (42).

ROLE OF NUCLEAR RECEPTORS IN HEPATIC INFLAMMATION AND FIBROSIS

Simple fatty liver is benign and nonprogressive in the majority of patients, and only about 10–20% of patients develop inflammation and fibrosis (NASH). This is important and relevant because inflammation and/or fibrosis determine the long-term prognosis of this disease. Inflammation is pivotal for the progression of chronic liver disease and the promotion of liver fibrosis and cancer. NASH could reflect a disease in which inflammation is followed by steatosis, or vice versa, in which NASH could be the consequence of a failure of antilipotoxic protection. In both situations, many hits derived from the gut and/or the adipose tissue may promote liver inflammation (43).

NRs can directly interact with proinflammatory transcription factors such as nuclear factor kappa B (NF-κB) and activator protein 1 (AP-1) (44). The activation of BA sensor FXR has an anti-inflammatory effect in the liver by interacting with NF-κB signaling (44, 45). In addition, GR represses Toll-like receptor (TLR)4- and TLR9-dependent transcription of inflammatory genes by disrupting p65/interferon regulatory factor (IRF) complexes required for TLR4- or TLR9-dependent transcription (46). PPARs play a key regulatory role in many processes, including metabolism, cell differentiation, and tissue inflammation. Activation of PPARα inhibits hepatic inflammatory responses and the transition from steatosis toward NASH and fibrosis through a direct, anti-inflammatory mechanism independent of its lipid handling properties (47). Similarly, activation of PPARγ is anti-inflammatory by inhibiting the phosphorylation of NF-κB, thus decreasing its transcriptional activities (48). PPARγ and LXRs cooperate with the GR to synergistically transrepress distinct subsets of TLR-responsive genes (46). Conversely, inflammatory processes can also alter RNA expression and protein modifications of NRs (46). LXRs by themselves can suppress LPS-induced expression of proinflammatory molecules by inhibiting NF-κB signaling, thus exerting an anti-inflammatory effect (49).

Fibrosis is characterized by accumulation of extracellular matrix (ECM) in the liver, and is a well-recognized feature in patients with chronic liver disease. Stellate cells and portal fibroblasts are demonstrated to be the key source of ECM in parenchymal liver disease (50). The intracellular signaling events controlling stellate cell activation include many regulatory factors, and the NR family is one among them. NRs such as FXR, PPAR, VDR, and LXR have been demonstrated to contribute to stellate cell activation (51–55). Thus, targeting NRs appears to be a potential treatment option in liver diseases that involve inflammation and fibrosis.

Nuclear Receptors as Therapeutic Targets in Hepatic Inflammation and Fibrosis

Farnesoid X Receptor. FXR agonists might be useful agents to lower inflammation in hepatocytes and prevent or delay cirrhosis and its progression to cancer in inflammation-driven liver diseases. WAY-362450, a synthetic potent FXR agonist, confers protection against NASH in mice fed a methionine- and choline-deficient (MCD) diet. Moreover, the elevations of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities induced by the MCD diet were decreased with WAY-362450 treatment. Although WAY-362450 treatment did not show any impact on hepatic TG accumulation, it significantly reduced inflammatory cell infiltration and hepatic fibrosis (56). Obeticholic acid (OCA, 6E-CDCA) is an FXR agonist that has been extensively studied in preclinical models of cholestasis, liver fibrosis, and diet-induced atherosclerosis. In a Phase II clinical trial in patients with T2D and NAFLD, OCA was well tolerated, it increased insulin sensitivity, and it reduced markers of liver inflammation and fibrosis (57, 58). OCA also improved endothelial vasorelaxation capacity in rat models of cirrhotic portal hypertension (58). Even though OCA met the primary endpoint of a reduction in serum alkaline phosphatase levels, safety data indicated that the drug exacerbated pruritus. A recent study shows that a decrease in OCA dose helps to overcome this side effect (59).

Liver X Receptor. LXR agonists also demonstrate promise in reducing inflammatory processes that accompany chronic inflammatory liver diseases such as NAFLD. LXR expression correlated with the degree of hepatic fat deposition, as well as with hepatic inflammation and fibrosis in NAFLD patients (60). Furthermore, GW3965 suppresses markers of fibrosis and stellate cell activation in primary mouse stellate cells (55).

Peroxisome Proliferator-Activated Receptors. Several PPARγ agonists have been demonstrated to be effective in the prevention of hepatic fibrosis. Hydroxysafflor yellow A (HSYA) is an herb-derived natural compound that is a PPARγ agonist and plays a pivotal role in the prevention of carbon tetrachloride (CCl_4)- and HFD-mediated liver fibrosis (61). Similarly, telmisartan, an AT1 receptor blocker and a partial PPARγ agonist, alleviates liver fibrosis induced by *Schistosoma mansoni* in mice (62). Curcumin, an active ingredient in turmeric, is another PPARγ agonist that inhibits portal myofibroblast proliferation in a mouse model of chronic cholangiopathy (63). Bezafibrate, a PPARα agonist, has an anticholestatic effect in the early-stage primary biliary cirrhosis (PBC) patients (64). Thiazolidinediones (pioglitazone or rosiglitazone), PPARγ agonists, demonstrate promising results in the treatment of hepatic fibrosis in that they inhibit collagen and fibronectin synthesis and hepatic stellate cell activation (65). Particularly, pioglitazone is in a Phase II clinical trial, in which the aim of the study is to evaluate whether long-term pioglitazone therapy can safely achieve and maintain biochemical and histological improvements in NASH. GFT505 is developed by GENFIT, a new liver-targeted drug candidate used to treat NASH as well as to reduce multiple cardiometabolic risk factors associated with the metabolic syndrome and T2D (66). This Phase II study is an ongoing study that will evaluate the efficacy and safety of GFT505 administered for 52 weeks on the reversal of NASH without worsening fibrosis.

Retinoid X Receptor. RXR agonists, all-trans retinoic acid (ATRA), and its metabolite 9-cis retinoic acid (9-cis RA), inhibit hematopoietic stem cell (HSC) proliferation and reduce profibrotic and proinflammatory genes transforming growth factor beta 1 (TGF-β1) and tumor necrosis factor alpha (TNFα), respectively (52, 67, 68). Consistent with this observation, RXR antagonist AGN193109 enhances HSC proliferation (52, 68, 69), which suggests that RXR agonists can be a potential therapeutic option for treating hepatic fibrosis.

Vitamin D Receptor. VDR protein is associated with the severity of both liver fibrosis and inflammation, and VDR ligands have the potential to prevent the cholestasis-induced inflammatory response. For instance, 1-alpha-hydroxyvitamin D (3) decreased the plasma levels of proinflammatory cytokines in bile duct ligated (BDL) mice (70) and 1,25 hydroxy-2 D(3) has antiproliferative and antifibrotic effects on liver fibrosis (71).

ROLE OF NUCLEAR RECEPTORS IN VIRAL HEPATITIS INFECTIONS

The hepatitis virus, hepatitis B virus (HBV) and hepatitis C virus (HCV), is the primary cause of serious illness, including acute and chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC) in humans. The viral-host interactions via several complex mechanisms result in inflammation, steatosis, fibrosis, altered lipid metabolism, insulin resistance, and HCC (72). NRs, through a variety of transcription factors, regulate HBV promoters and enhancers and thereby control viral pregenomic RNA synthesis and transcription. It is important to note that antiviral strategies to treat viral hepatitis can take advantage of the NR's role in disease progression. Currently, studies demonstrate that the HBV protein X (HBx) of HBV and HCV core protein induces activity of LXRα, SREBP-1c, and PPARγ in the hepatocytes, thus stimulating lipogenesis in the liver (73). Furthermore, replication of HCV is linked to the FA biosynthetic pathway mediated by LXRα; activation or inhibition of LXRα resulted in an increase or decrease in HCV RNA expression, respectively (74). In line with this concept, PGC1α, a major metabolic regulator of key gluconeogenic genes, activates HBV transcription. Short-term fasting, which activates gluconeogenesis by way of PGC1α, also markedly induces HBV gene expression. This induction is completely reversible by refeeding, which suggests that nutritional signals may impact HBV replication (75). BAs promote transcription and expression of both HBV and HCV RNA through the NR FXR (76, 77). In addition, the orphan NR SHP is also shown to be involved in the BA-mediated regulation of HBV gene expression. The BA-mediated HBV gene expression offsets the antiviral effect of interferon γ (IFN-γ) (77).

Nuclear Receptors as Therapeutic Targets in Viral Hepatitis Infections

Peroxisome Proliferator-Activated Receptors. Even though data suggest that HBx protein induces PPARγ (which is lipogenic and linked to HCV replication) activity in hepatocytes (73), the PPARγ agonist rosiglitazone reduced the amount of HBV DNA, hepatitis B surface antigen, and hepatitis B antigen in the culture supernatant (78). In addition, preliminary human data demonstrate beneficial effects of PPARα and PPARγ agonists on viral load and liver enzymes (79). PPARα agonist bezafibrate is effective in patients with advanced chronic hepatitis C, evidenced by reduced liver enzyme activity (80). Although the mechanism of protection is not entirely clear, these data suggest that PPARs may represent new therapeutic targets for combating HCV infection.

ROLE OF NUCLEAR RECEPTORS IN CHOLESTATIC LIVER DISEASE

The main feature of cholestatic liver disease is an accumulation of BAs in the liver that eventually spill over to systemic circulation. The accumulation of potentially toxic BAs in the liver leads to cellular damage that is exacerbated by inflammation; this ultimately leads to hepatic fibrosis. Depending on the persistence of etiology, disease severity, and duration, hepatic fibrosis may result in liver cirrhosis and hepatocellular or cholangiocellular cancer (81). Because of the toxic nature of BAs, their synthesis, transport, and metabolism are tightly regulated in the liver by an

intricate network of NR-regulated pathways. For instance, those that are pertinent to regulation of hepatobiliary homeostasis, bile synthesis, and bile secretion include the FXR, SHP, PXR, and VDR. As regulators of inflammation, fibrosis, and energy homeostasis, NRs such as GR, PPARα, and PPARγ can also contribute to cholestatic liver disease. Furthermore, other biliary constituents such as bilirubin can also activate NRs such as the CAR (81). Understanding NR function therefore not only increases our understanding of the physiology and pathophysiology of BA metabolism, but also can lead to development of NR ligands for the treatment of cholestasis.

FXR is a master regulator of bile salt (BS) homeostasis, because it promotes transcription of bile salt export pump (BSEP) that mediates the rate-limiting step in hepatocellular BS excretion through the transport of BAs across the canalicular membrane in humans, mice, and rats (82). Mutations in BSEP result in a progressive familial intrahepatic cholestasis type 2, which is characterized by impaired bile flow and irreversible liver damage (83). On the contrary, FXR variants are identified in only a few cholestatic syndromes (81, 84). Interestingly, many reports demonstrate alterations in transcriptional coactivators of FXR in cholestatic liver diseases. For instance, PGC1α expression is repressed in patients with gallstones (85). This suggests that PGC1α-associated reduction of FXR activity could contribute to altered bile composition and gallstone formation through inhibition of target genes BSEP and MDR3 (81). Thus, pharmacological stimulation of BSEP or FXR presents as a potential therapeutic option for treating cholestatic liver diseases. FXR also represses transcription of CYP7A1 (an enzyme that mediates rate-limiting step in conversion of cholesterol to BAs) through SHP (86–88). FXR induces Fgf-15 in the small intestine and represses Cyp7a1 in liver through a mechanism that involves FGF receptor 4 (FGFR4) and SHP (89). In addition to FXR, genetic variants of PXR are also associated with increased susceptibility to cholestatic liver disease such as intrahepatic cholestasis of pregnancy (ICP) and primary sclerosing cholangitis (PSC) (90, 91). An increased expression in PXR and CAR is also evidenced in patients with obstructive cholestasis, and the expression decreases in late-stage cholestasis for limiting the progression of liver injury (92). Transcription factor E2F1 contributes to cholestatic liver fibrosis via SHP-mediated regulation of Egr-1 that involves HNF4α and EID1 (36, 93, 94).

Nuclear Receptors as Therapeutic Targets in Cholestatic Liver Disease

Farnesoid X Receptor. FXR is the major NR involved in the regulation of processes that support BA formation, transport, and detoxification. The main function of FXR is to limit hepatocellular BA overload. Therefore, FXR can be an ideal therapeutic target for treating cholestatic diseases. OCA, which is used to treat liver fibrosis (discussed previously), is a modified BA and FXR agonist that is derived from the primary human BA chenodeoxycholic acid. OCA is efficacious in alleviating ALT levels as well as pruritus in PBC patients (59). A Phase IIIb clinical trial to assess the effect of OCA on clinical outcomes in PBC patients is already in progress. INT-767, a dual FXR and the membrane G protein–coupled receptor (TGR5) agonist, results in improvement in liver injury in a mouse model of chronic cholangiopathy by reducing BA synthesis via the induction of ileal Fgf15 and hepatic *Shp* gene expression (95). These reports uphold the usefulness of FXR agonists in the treatment of cholestatic liver disease.

Pregnane X Receptor. The PXR agonists atorvastatin and pregnenolone-16α-carbonitrile stimulate hepatic BA/bilirubin metabolizing and detoxifying enzymes and key hepatic efflux systems; thus, they stimulate hepatic BA and bilirubin detoxification and elimination pathways in mice (96). But atorvastatin in PBC patients does not improve cholestasis (97), which suggests lack of effectiveness of PXR agonists in the treatment of cholestatic liver disease. Yin Zhi Huang, a decoction of Yin Chin (*Artemisia capillaris*) and three other herbs, is widely used in Asia to prevent and treat

neonatal jaundice. It is demonstrated that CAR mediates the effects of Yin Zhi Huang on bilirubin clearance in mice (98).

Constitutive Androstane Receptor. 6-(4-Chlorophenyl)imidazo[2,1-b][1,3]thiazole-5-carbaldehyde-*O*-(3,4-dichlorobenzyl) oxime (CITCO), a CAR activator, also protects against cholestasis (99). In addition, CAR agonists phenobarbital and 1,4-bis-[2-(3,5-dichlorpyridyloxy)]benzene reduced serum bilirubin and BA levels in healthy as well as in BDL mice (96). Although promising, the efficaciousness of CAR agonists in the treatment of cholestatic liver disease calls for more research.

ROLE OF NUCLEAR RECEPTORS IN LIVER REGENERATION AND HEPATOCELLULAR CANCER

BAs and BA-mediated FXR-dependent pathways are required for normal liver regeneration (100). Given the role of BAs and FXR in liver regeneration, it is intriguing that FXR is also important for HCC formation. FXR knockout mice develop HCC (101). Similar to FXR, its downstream target, SHP, has demonstrated downregulation in human HCC (102). Tumor suppressive functions of SHP include inhibition of HCC cell proliferation and activation of HCC cell apoptosis (103); the latter involves SHP interaction with Bcl2 in the mitochondria (104). The FXR/SHP pathway negatively regulates Sirtuin 1 (SIRT1), and increased expression of SIRT1 is associated with HCC (105). SHP negatively regulates tumorigenesis, both in vivo and in vitro, by inhibiting cyclin D1 expression and cellular proliferation (106). In addition, SHP modulates DNA methylation by repressing DNA methyltransferase (DNMT) expression and function (107, 108). SHP also interacts with P53 and murine double minute 2 (MDM2) to dictate their protein stability and function (109–111).

CAR activation produces a strong and rapid proliferative response in mouse liver by stimulating cyclin D1, which plays a critical role in cell cycle progression in proliferating hepatocytes (112). Furthermore, CAR expression is higher in the developing liver than in the adult liver (113). This suggests that CAR agonists present as a potential treatment option during liver transplantation. Furthermore, CAR activation is also associated with phenobarbital-induced hepatocyte proliferation and tumorigenesis (114, 115). However, CAR expression levels are reduced in HCC (113). The reason for this discrepancy is not clear. Shedding more light onto this might increase our understanding of the usefulness of CAR ligands to treat hepatocellular cancers.

PPARα modulates the activities of all three interlinked hepatic FA oxidation systems, including the mitochondrial and peroxisomal β-oxidation and microsomal ω-oxidation pathways. Hyperactivation of PPARα, by both exogenous and endogenous activators, upregulates hepatic FA oxidation, which results in excess energy burning in liver, thereby contributing to the development of liver cancer in rodents (116). The mechanism involving PPARα-mediated hepatocarcinogenesis includes generation of reactive oxygen species, oxidative stress, and hepatocellular proliferation (116). PXR plays a role in liver regeneration by way of modulating the lipid accumulation in the proliferating hepatocytes (117).

Accumulating evidence suggests that the tumors produce endogenous ligands of LXRs, oxysterols that inhibit a robust immune response to escape from immune surveillance (118). Despite accumulation of endogenous ligand of LXR in cancer, activation of LXR seems protective via IFN-γ expression, which limits tumor growth (118). It is therefore necessary to obtain complete knowledge of how the LXRs work in all the different immune and inflammatory settings to elucidate

the detailed functions of the LXRs in these pathways. This in turn is important to avoid side effects associated with LXR agonists.

Nuclear Receptors as Therapeutic Targets in Liver Regeneration and Hepatocellular Cancer

Farnesoid X Receptor. BAs are mitogens that drive hepatocellular proliferation. The activation of FXR with the agonist GW4064 results in protection against cisplatin-induced toxicity (chemoprotection) as well as chemoresistance (119). By contrast, downregulation of FXR by miR-421 promoted the proliferation, migration, and invasiveness of the cancer cell line (120, 121). This mechanism needs further investigation for the FXR agonist or antagonist to be considered for HCC treatment. But the potential for FXR agonists during liver transplantation in which hepatocellular proliferation is required should not be overlooked.

Peroxisome Proliferator-Activated Receptors. The PPARα agonist bezafibrate inhibits serine palmitoyltransferase (SPT), a key enzyme in de novo sphingolipid biosynthesis. SPT activity plays an important role in initiation of liver regeneration after partial hepatectomy (PHT), and its inhibition by bezafibrate negatively affects liver regeneration, presumably by decreasing the availability of plasma-borne FAs (122). The use of PPARγ agonist thiazolidinediones (pioglitazone and rosiglitazone) is associated with a decreased liver cancer incidence in T2D patients (123, 124). The association with individual sites of specific cancer differs between pioglitazone and rosiglitazone, and the underlying mechanisms require further investigation.

NUCLEAR RECEPTORS IN DRUG-INDUCED LIVER DISEASE

Liver is the site of first-pass metabolism; thus, it is inherently exposed to high concentrations of xenobiotics and other chemicals before delivery to the systemic circulation. All phases of hepatic drug metabolism and disposition are controlled by NRs. The major sensors of lipophilic xenobiotics and drugs include CAR and PXR, and among these, PXR is regarded as a master xenobiotic sensor, which can bind to various structurally diverse chemicals to rapidly induce the expression of drug metabolizing enzymes and transporters, ultimately leading to the detoxification of xenobiotics (125). Recently, FXR antagonism by NSAIDS was demonstrated to be the key molecular mechanism of drug-induced liver injury (DILI) through systematic network analysis and in vitro assays (126). Acetaminophen (APAP) hepatotoxicity is a prototypic example for drug interactions due to NR activation. CAR, PXR, and RXRα activation results in sensitization to APAP-induced hepatotoxicity by induction of phase I enzymes, Cyp1a2 and Cyp3a11, which can convert APAP to cytotoxic metabolite (127–129). On the contrary, activation of FXR induces enzymes involved in glutathione (involved in detoxification of metabolite) synthesis and thus protects against APAP-induced hepatotoxicity (130). Similarly, LXR activation also protects against APAP toxicity by suppression of phase I enzymes, activation of phase II (conjugation reaction) enzymes, and induction of enzymes involved in glutathione synthesis (131). Other nuclear factors involved in drug metabolism and the defense against oxidative stress are the aryl hydrocarbon receptor (AhR) and nuclear factor-E2-related factor (Nrf2). Nrf2 has been demonstrated to affect DILI by preventing protein adduct formation, reactive oxygen species accumulation, and glutathione depletion. Other factors that result from Nrf2 activation that contribute to liver defense mechanisms include improvement in liver detoxifying enzymes and induction of transport proteins that mediate chemical efflux processes (132). Even though targeting Nrf2 presents as a potential

treatment option for treating DILI, Nrf2 enhancers are not yet currently used in clinical trials to test their efficacy for treating liver disorders.

Nuclear Receptors as Therapeutic Targets in Drug-Induced Liver Disease

Farnesoid X Receptor, Constitutive Androstane Receptor, Pregnane X Receptor, Peroxisome Proliferator-Activated Receptor, and Liver X Receptor. Depending on the mechanism of action, xenobiotic agents can instigate liver injury in a variety of ways. In general, they can initiate an inflammatory response, and they can alter drug-metabolizing enzymes, reactive-intermediate formation, and protein adduct accumulation. NRs control aforementioned responses and thus are potential targets for DILI. Activation of FXR by GW4064 results in a protection against cisplatin-induced as well as APAP-induced hepatotoxicity (119, 130). An agonist of CAR, 1,4-bis[2-(3,5-dichloropyridyloxy)] benzene (TCPOBOP), abated acute and chronic concanavalin A–mediated liver injury and fibrosis in mice (133). Surprisingly, CAR activation by neonatal exposure to TCPOBOP led to persistently induced expression of the CAR target genes, and mice showed a permanent reduction in sensitivity to zoxazolamine treatment as adults (134). But activation of CAR exacerbates APAP-induced hepatotoxicity (127). Similarly, PXR activation also exacerbates APAP-induced hepatotoxicity (128). Thus, compounds inhibiting CAR and PXR may represent promising therapeutic approaches for the treatment of APAP-induced liver injury. In fact, a PXR antagonist (FLB-12) attenuates APAP hepatotoxicity in mice (135). A PPARα agonist (clofibrate) and LXR agonist (TO1317) have also demonstrated protective properties against APAP-induced hepatotoxicity (131, 136). Taken together, this information indicates that NRs play a central role in drug interactions and in DILI.

Small Heterodimer Partner in Noncoding RNA Regulation and Its Potential as a Drug Target. MicroRNAs (miRNAs) are small noncoding RNA transcripts that regulate gene expression and thus modulate cellular pathways. Our recent reports advanced the current knowledge on miRNA regulation by SHP. SHP controls the expression of miR-433 and miR-127 via interaction with ERRγ (137–139) to mediate HCC cell migration via MMP13 (140) and cAMP response element–binding protein (CREB) (141). SHP modulates miR-206 expression, which in turn targets Notch3 to activate apoptosis. This suggests that miR-206 may function as a tumor suppressor and is a potential target for cancer therapy (142–144). SHP also inhibits miR-200c expression that involves PPARα and LRH-1 (145).

In addition to its regulation of miRNAs, SHP functions as an important regulator of long noncoding RNA (lncRNA) expression and function. SHP represses the expression of H19, and during conditions in which SHP is repressed by Bcl2, H19 levels increase, which leads to hepatic fibrosis (Y. Zhang, C. Liu, O. Barbier, R. Smalling, H. Tsuchiya, S. Lee, D. Delker, A. Zou, C.H. Hagedorn & Li Wang, manuscript under review). Because SHP plays a central role as a transcriptional repressor in regulating BA and cholesterol homeostasis, on the basis of what is known of its structure, SHP would be an intriguing target (6). The structure of SHP has so far proven difficult to determine owing to solubility issues (146). Even though the researches in this study overcame the difficulties by using a maltose binding protein (MBP) fusion strategy, removal of helices H1 and H2 in the LBD rendered the protein highly soluble. Nonetheless, the authors conclude that SHP has two cofactor-binding sites, one that is ligand-dependent (potentially druggable) via the C-terminal AF-2 site and another that is ligand-independent via the EID1-binding site near the helix H1 pocket. Although this study provided new insights into the structure of SHP, no potential ligands were identified. Thus, identifying both natural and synthetic ligands for SHP may hold promise for developing potential drug targets (**Figure 2**).

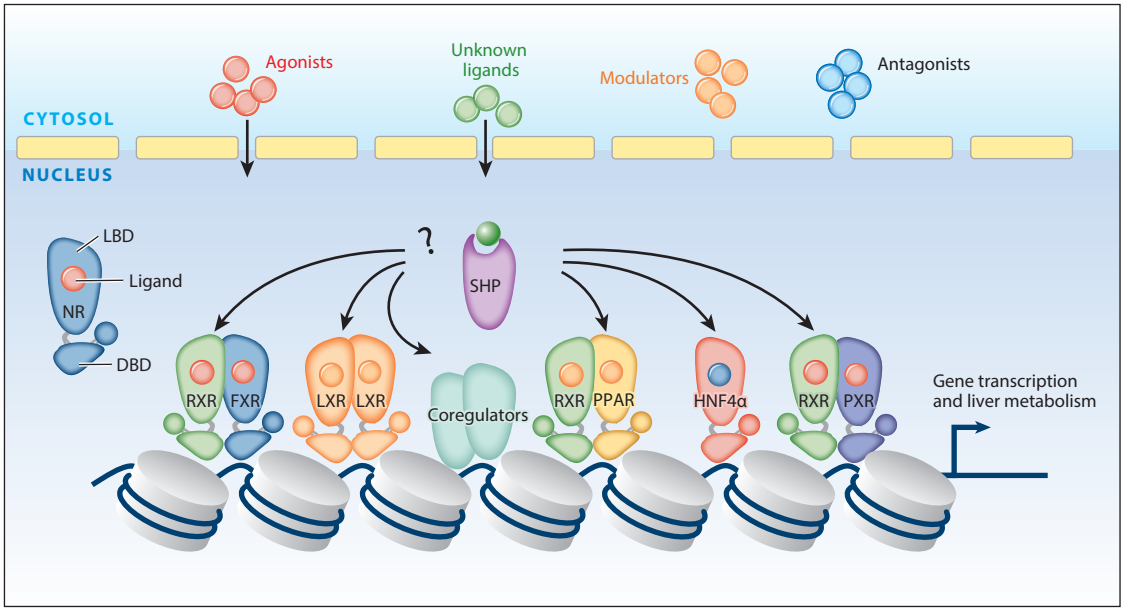

Figure 2

Metabolic NRs (FXR, LXR, PPAR, PXR, and HNF4α) are presumed to sense and respond to small lipophilic ligands (agonists and antagonists) and metabolic intermediates (modulators), as a monomer, a homodimer, or a heterodimer (usually with RXR). Upon binding to ligands or other modulators, these NRs bind to their cognate sequence-specific NRRE in regulatory regions of their target genes. NR DBD contributes to response element selection, whereas LBD contributes to dimerization and determines ligand-regulated interactions with coregulators. The orphan nuclear hormone receptor SHP interacts with a number of metabolic NRs and functions as a major transcription repressor that controls liver metabolism. Many NRs have well-characterized natural ligands and synthetic drugs, but the ligand for some of the NRs such as SHP is yet unknown. Discovery of more specific and new NR-targeting drugs will offer promise for better treatment of liver disorders in which NRs play a central role. Abbreviations: DBD, DNA binding domain; FXR, farnesoid X receptor; HNF4α, hepatic nuclear factor-4-alpha; LBD, ligand-binding domain; LXR, liver X receptor; NR, nuclear receptor; NRRE, nuclear receptor response element; PPAR, peroxisome proliferator-activated receptor; PXR, pregnane X receptor; RXR, retinoid X receptor; SHP, small heterodimer partner.

CONCLUSION

NRs control several important hepatic functions involved in the pathophysiology of liver injury and disease. Novel concepts related to NRs and liver physiology have been successfully integrated into the drug development process to develop effective therapies. Currently, there are many PPAR and FXR agonists that are going through Phase II or later stages of clinical trials with promising results. Despite the expanding use of NR targeting as therapy, there are many unknowns with regard to some classes of NRs, such as orphan NRs, whose functions have proven important but do not have any identified ligands. Expansion of the current knowledge in addition to translation of the existing knowledge on NRs should result in the development of effective therapies that stand to benefit from such novel NR-directed approaches.

DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

AUTHOR CONTRIBUTIONS

S.R. and X.Z. prepared the text, table, and figures. L.W. supervised and finalized the manuscript.

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