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NUCLEAR RECEPTORS, INFLAMMATION AND LIVER DISEASE: INSIGHTS FOR CHOLESTATIC AND FATTY LIVER DISEASES

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Summary

Members of the nuclear receptor (NR) superfamily of ligand-activated transcription factors are players of substantial relevance in the regulation of hepatic gene expression. NRs direct normal physiology and metabolism, adaptations to liver disease, responses to inflammation and toxins, and contribute to the regenerative response. Here we summarize current experimental and clinical data focusing on roles for NRs in cholestasis and non-alcoholic fatty liver disease (NAFLD), highlighting NRs as potential targets for safe and effective therapeutic interventions.

INTRODUCTION

Inflammation (Latin, *inflammatio*, a setting on fire) is a complex biological response to a variety of injurious stimuli (1). Due to its strategic position in the body, the liver plays a key role during systemic inflammation being both a main player, due to its ability to secrete a number of proteins that regulate the acute phase response (APR), as well as a target of inflammation (2, 3). In addition, virtually all liver diseases are accompanied by some degree of hepatic inflammation. The mechanisms and mediators vary depending of the nature of the injury (acute vs. chronic, viral vs. toxic or autoimmune or metabolic, etc.) but generally lead either to complete resolution, or to activation of fibrogenic and apoptotic pathways, the balance of which may determine disease progression to end-stage liver disease (3). Significant advances has been made in recent years in deciphering the molecular mechanisms underlying both the liver response to systemic inflammation as well as the intricacies of hepatic injury, local inflammation, cell death and repair (3, 4). One area of particular interest is the role of ligand-activated transcriptional regulators (members of the nuclear receptor [NR] superfamily) as both active players and potential targets in both systemic and hepatic inflammation (5–7). The present article aims to summarize the current knowledge on NRs and their potential role in two relevant settings associated to

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Members of the nuclear receptor superfamily are mentioned by their common name followed by the official name (as proposed by the Nuclear Receptors Nomenclature Committee *Cell* 1999;97:161–163) in brackets. The same convention is adopted when referring to hepatobiliary transporters where the approved gene symbol (following the Human Genome Nomenclature Committee Guidelines [<http://www.genenames.org/index.html>]) is in brackets preceded by the common name or aliases.

inflammation: inflammation-induced cholestasis and non-alcoholic fatty liver disease (NAFLD).

BASIC CONCEPTS ON NR FUNCTION

NRs are multifunctional ligand-activated transcriptional regulators that are perfectly poised to be the mediators between extracellular signaling, and cellular responses to injury. These are ancient proteins that are present in all animals, but not clearly present in prokaryotes or yeast (8). NR structural protein domains are organized along the following paradigm: an N-terminal activating domain, a DNA binding domain, a large and variable ligand binding domain (LBD), and a C-terminal activating function. These multi-partite transcription factors interact with dozens of proteins, but have a unique LBD, that is essentially the main defining feature of this family of transcriptional regulators (7). After binding of an agonist to the LBD a conformational change in the NR occurs, typically transforming a quiescent transcription complex (one that is bound by a corepressor) by unloading the co-repressor, to an active one by recruiting a co-activator. After this coregulator exchange, more components of the transcriptional complex join, including RNA Polymerase II, leading to mRNA transcription.

There are 48 members of the NR superfamily in humans, of which at least a dozen participate in metabolic functions of the liver. The NR ligands are as diverse as fatty acids, bile acids, drugs, toxins, and intermediary molecules in metabolism. It should be no surprise that binding of ligands to NR LBDs serves to “sample” the intracellular environment of the hepatocyte, change gene expression, eliciting a shuttling of regulators onto (or off) transcription complexes. All together, this changes the transcriptional profile of hepatocytes in response to their environment by responding to the potency of various small molecules as NR LBD occupants.

INFLAMMATION-INDUCED CHOLESTASIS: THE ROLE OF NRs

Given the liver's central roles in metabolism, handling of ingested molecules, and main source of serum proteins involved in the APR, it is not surprising that many of these core liver functions change significantly in the setting of inflammation, and that this is due to modifications in NR-regulation of target genes (9, 10). One of these NR-regulated functions that appear to be a stereotyped and predictable response to inflammation is a reduction in bile flow, a hallmark of cholestasis (9). Inflammation-induced cholestasis occurs mostly in patients suffering from sepsis due to gram-negative bacteria, but has also been reported in other clinical settings including alcoholic hepatitis, viral or drug-induced hepatitis, and paraneoplastic syndromes (10). Interestingly, cholestasis, much like the other components of the APR, does not require liver damage, or cellular infiltration—rather, it is a response of hepatocytes to circulating molecules leading to activation of intracellular signaling pathways that change gene expression. These circulating molecules include cytokines (primarily interleukin-1 β , Tumor Necrosis Factor α and interleukin -6), chemokines, as well as those involved in innate immunity and the activation of Toll like receptors (e.g. lipoteichoic acid or lipopolysaccharide receptors) (11, 12). Recent evidence from several groups support a general paradigm whereby a confluence of signals from these circulating molecules lead to

altered hepatic gene expression due to inflammation-induced alterations in the RNA expression, and post-translational modification of critical NRs and coregulators. Affected target genes include most of those involved in bile acid synthesis, transport and metabolism, organic anion transport, and detoxification. For example, reductions in the nuclear concentrations of the central heterodimer member retinoid X receptor α (RXR α ;NR2B1) in response to inflammation leads to reduced expression of a wide variety of bile acid transporters, organic anion transporters, and metabolic genes—all resulting in an impairment in bile flow. This general paradigm has been delineated in several rodent models of lipopolysaccharide-induced cholestasis as well as from supportive data in sepsis and human liver diseases.

Essentially all aspects of bile formation and physiology are regulated by NR family members (11, 12). These include bile acid synthesis, import, conjugation, and export, as well as phospholipid and sterol transport and metabolism and organic anion flux. With regards to bile acids, the main genes responsible for bile acid transport (import via the Na⁺/Taurocholate Cotransporting Polypeptide [Ntcp, Slc10a1]) and export (via the Bile Salt Export Pump [BSEP, Abcb11]) are rapidly and profoundly suppressed in inflammation, leading to >80% reduction in RNA and protein levels for these transporters (9). Depending upon the species, and gene target, this can be due to reduced levels of the Hepatocyte Nuclear Factor 4 α (HNF4 α [NR2A1]) as well as post-translational alterations of RXR α (13–15). Also, the FXR, farnesoid X receptor (NR1H4), which serves as an intracellular bile acid sensor may participate in promoting the downregulation of *Ntcp* via its target gene the short heterodimer partner, SHP (NR0B2). Interestingly, stimulation of alternative bile acid export through the induction of the basolateral transporters multidrug resistance protein 3 and 4 (Mrp3 [Abcc3], Mrp4 [Abcc4]) has been described in the setting of endotoxin-induced and other experimental models of cholestasis (16). This may play an important role in the hepatocellular clearance of cholephilic substances that accumulate inside the cell in the setting of cholestasis since provide an alternative excretion route for bile acids and other organic anions into the systemic circulation. A summary of available information on the role of selected NR in inflammation induced cholestasis is shown in Table 1. For an in-depth review the reader is referred to recent reviews on the subject (10, 12, 17).

In addition to direct changes in governing NR RNA expression and post-translational modification of NR proteins induced by inflammatory signaling, there are direct interactions between nuclear inflammatory mediators and NRs that alter target gene expression. For example NF- κ B and FXR, one of the main NRs for bile acids, mutually inhibit each other in gene-specific ways (18, 19). Similar interactions are seen for various components of inflammatory signaling (JNK, c-jun, PI₃K) and a variety of NRs (liver X receptor [LXR, NR1H3], (Pregnane X receptor [PXR, NR1I2] and glucocorticoid receptor [GR, NR3C1] among others). This suggests that there are layers of interactions between innate immunity and NR signaling that take place within each hepatocyte, of which reduced bile flow is but one component. And as such, help integrate adaptation to inflammation by directly targeting crucial gene regulators.

NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD): LIPOGENESIS, INFLAMMATION AND NUCLEAR RECEPTORS

The accumulation of fat in the liver (steatosis) can occur by many mechanisms. The commonest causes are linked to alcohol consumption and to the metabolic derangements seen in overweight and obese people with insulin resistance and/or diabetes termed NAFLD. NAFLD is the most common liver diseases worldwide with an estimated prevalence of 10–24 % in the general population, more so in populations reliant upon Western-style diets (23, 24). NAFLD refers to a histological spectrum including various degrees of steatosis, inflammation and fibrosis of the liver. While simple hepatic steatosis has benign clinical course the presence of inflammation defines the aggressive form of the disease [Nonalcoholic steatohepatitis (NASH)] which is deemed at high-risk for developing more advanced fibrosis, cirrhosis and hepatocellular carcinoma (20, 21). Which are the underlying mechanisms explaining why some individuals with NAFLD transit towards hepatic inflammation and develop an aggressive form of the disease (i.e. NASH) remain unknown

The pathogenesis of NAFLD is generally viewed as two-step process. The first step is hepatocyte accumulation of triglycerides (TG) and associated lipids. The second step is the occurrence of liver inflammation (which defines NASH) that is presumably the driving force for cell death and disease progression (22). It is widely accepted that the presence of insulin resistance (IR) has a central role in TG accumulation in liver cells (23). Several studies have shown that NAFLD patients exhibit evidence of IR at the level of muscle, white adipose tissue (WAT) and liver. Impaired peripheral insulin action is associated to an uninhibited WAT lipolysis which results in an increased flux of fatty acids (FA) to the liver. FA are then taken up by hepatocytes and packaged in the form of droplets of triglycerides inside the cell (24). IR also causes compensatory hyperinsulinemia which in turn determines an enhanced *de novo* hepatic lipogenesis thus contributing to TG accumulation (22).

The cellular and molecular mechanisms underlying IR are only partially understood [for review see (25)]. A relevant role of fat-secreted hormones (collectively termed adipokines or adipocytokines [mainly adiponectin, leptin and tumor necrosis factor α (TNF α)] has been recently recognized as a key factor of obesity and overweight-associated IR (26). Recent evidence indicate that inflammatory events occurring in the adipose tissue are key initial events in promotion IR through adipokine imbalance (27).

The current notion for disease progression is that hepatocytes possess a given capacity to store FA as TG that once overwhelmed, lead to cell damage. The excess of free FA inside the cell would be the culprit of triggering the production of reactive oxygen species (ROS) causing lipotoxocity and activation of inflammatory signaling pathways and ultimately cell death by necrosis and/or apoptosis (28). If this view is correct, a subgroup of patients may be directly committed to NASH from the beginning of the disease depending of their hepatic TG storing capacity.

Available information on inflammatory mediators in NASH has been largely generated in animal models and their role in human NAFLD has not yet been studied (22). Current data indicates that a complex cross-talk between parenchymal and non-parenchymal cells via a

number of soluble mediators takes place in experimental NASH. In addition to resident cells (hepatocytes, activated Kupffer cells and hepatic stellate cells) circulating leucocytes become engaged in the local inflammatory process, via expression of adhesion molecules. Among the main mediators of inflammation in NASH are TNF α and other fat-derived cytokines, interleukins 1 and 6 as well as the IKKb-NFkB and the c-Jun N-terminal kinase (JNK) pathways which act as downstream players promoting disease progression through inflammation, cell death and hepatic fibrogenesis (29, 30).

The role of NRs in mediating pathophysiological phenomena in NAFLD has not been extensively characterized. However, some members of the NR family are key regulators of hepatic lipogenesis and also of both hepatic and systemic inflammation (31). In virtue of that, they are critically involved in steatosis development and the occurrence of NASH. For example, the role of members of the PPARs (peroxisome proliferator-activated receptors) family in regulating inflammatory and metabolic signaling in NAFLD has been well delineated and they are currently major therapeutic targets in this disease (32, 33). Data on the role of other NRs such as FXR, PXR and CAR in NAFLD is emerging (34–36) and promising, considering the fact that these receptors are major players in the adaptive response of the cell when facing oxidative stress or the accumulation of toxic endo- or xenobiotics. Available information on selected NRs involved in these pathways is shown in Table 2. For a more comprehensive review the reader is referred to recent papers on the subject (33, 37).

CURRENT & POTENTIAL ROLE FOR NR MODULATION IN CHOLESTASIS AND FATTY LIVER

As mentioned earlier, modulation of NR is a promising avenue in the treatment of several liver diseases (33). In the case of cholestasis, current data from experimental models, including inflammation-induced cholestasis, suggest that agents with the ability to enhance cell defense mechanisms against the accumulation of toxic compounds, retained intracellularly during cholestatic injury, likely would be useful in preventing hepatocellular damage and disease progression (12). However, the therapeutic benefits or risks of targeting NR actions require further investigation and physiological understanding. Attention needs to be paid to differences between rodents and humans and also to the pleiotropic effects of modulating NR. Moreover, it is likely that the effects of modulating the hepatocellular adaptive response may differ depending on the stage of the disease (33). Based on experimental data, the most promising targets are CAR, PXR and FXR although other members of the NR family are amenable of being targeted [for an in-depth review see ref. (12)]. Drugs that target CAR (e.g., phenobarbital) and PXR (e.g., rifampicin) have already been used in the treatment of cholestasis before their effects NR were discovered. New compounds with more selective action and increased potency need to be developed and assessed in the setting of cholestatic injury. With regard to FXR, experimental data using FXR agonists have shown some hepatoprotective effects in cholestatic rat models. Moreover, a phase II clinical trial assessing the effects of 6E-CDCA in primary biliary cirrhosis (a prototypic cholestatic liver disease) is currently ongoing (38) and its results regarding efficacy and safety are eagerly awaited.

In the case of NAFLD, the use of NR activators as a treatment strategy holds promise. Since there are commercially available, ligands of both PPAR α (fibrates) and PPAR γ ligands (e.g., thiazolidinediones [TZDs]) have been studied in NAFLD. Fibrates have been tested in small studies without significant effects (33). On the other hand, TZDs are the most widely studied drugs in this setting. Pilot and controlled studies using pioglitazone and rosiglitazone, have shown that they are markedly effective in reducing liver fat content by 30–50% and sensitizing the liver to insulin (32, 39). These positive effects translate in a reduction in the serum levels of aminotransferases, steatosis, inflammation and even fibrosis improvement in patients with NAFLD/NASH. Although no serious side effects occurred in these, a consistent finding is the occurrence of modest weight gain. Due to the fact that first generation TZDs proved to be hepatotoxic there is some concern with the long term use. However, they have been tested in a substantial number of patients in the diabetes field without significant effects in this regard. Current data most is still insufficient to firmly recommend TZDs as treatment of NASH as published studies [reviewed in (33)] do not include large number of patients and the reported follow-up is short for a slow-evolving disease. Larger studies are underway and their results are eagerly awaited.

Finally, activation of FXR with the synthetic agonist INT-747 is already in a preclinical phase (38, 40, 41). Data of a phase II study in type 2 diabetic patients with NAFLD shows that single oral daily dose of INT-747 statistically significantly improved glucose disposal rate, assessed by euglycemic clamp, which is consistent with an improved hepatic and peripheral insulin sensitivity (42). Thus, FXR agonists are promising agents for the treatment of NAFLD.

SUMMARY AND OUTLOOK

In recent years, we have witnessed the accumulation of a growing body of evidence showing that NRs are of overwhelming relevance as regulators of hepatic gene expression. NRs play a central role in the control of carbohydrate and lipid metabolism in the liver and other tissues as well as critically regulate genes responsible of endo- and xenobiotic detoxification. A complex network involving several members of the NR family including FXR, PXR, vitamin D receptor, CAR, the PPARs, LXRs and others target an overlapping set of genes and control bile acid synthesis and transport as well as lipogenesis, fatty acid oxidation and gluconeogenesis pathways. Moreover, some NRs play major roles as inducers and regulators of both systemic and hepatic inflammation. Therefore, direct or indirect targeting of these NR-dependent hepatic pathways may be helpful for pathological processes such as diabetes, hyperlipidemia, cholestasis and NAFLD. NRs critically regulate the expression of hepatobiliary transport systems in both basal conditions and in pathological situations such as inflammation, which is a common phenomenon in every liver disease. NR modulation through ablation or overexpression has relevant effects in experimental settings such as inflammation-induced cholestasis. On the other hand, NR modulation markedly influences hepatic lipid and carbohydrate metabolism and the development of hepatic steatosis and steatohepatitis in experimental models. This data supported the role of NRs potential targets for intervention in both cholestasis and NAFLD. Some agents such as PPARs agonist are already available and showed some efficacy in the clinical setting of NAFLD. The recent availability of synthetic agonists of FXR has prompted the launch of

clinical trials that are currently underway. Although more preclinical data are needed, CAR and PXR agonist could also have beneficial effects in the clinical setting of cholestasis and perhaps NAFLD/NASH. Thus, modulation of NR function is a promising therapeutic approach in a number of liver diseases. The place and usefulness of the NR-targeted therapy in the care of our patients remains to be determined, but with the new era of available agents, will soon be one for evaluation, rather than delegated just to the previous role as potential therapeutics.

Abbreviations used in this paper

NR	nuclear receptor
NAFLD	non-alcoholic fatty liver disease
APR	acute phase response
LBD	ligand binding domain
Ntcp	Na ⁺ /Taurocholate Cotransporting Polypeptide
BSEP	Bile Salt Export Pump
HNF4α	Hepatocyte Nuclear Factor 4 alpha
RXRα	retinoid X receptor alpha
SHP	short heterodimer partner
Mrp3	multidrug resistance protein 3
FXR	farnesoid X receptor
PXR	pregnane X receptor
CAR	constitutive androstane receptor
LXR	liver X receptor
GR	glucocorticoid receptor
NASH	Nonalcoholic steatohepatitis
TG	triglycerides
WAT	white adipose tissue
FA	fatty acids
IR	insulin resistance
JNK	c-Jun N-terminal kinase

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Table 1

Summary of data on the role of selected nuclear receptors in inflammation-induced and other forms of cholestasis^{*,#}.

NR member	Main function	Effects of activation/deactivation relevant for cholestasis
FXR (farnesoid X receptor, NR1H4)	Intracellular bile acid sensor	FXR is activated by bile acids. Its activation, via direct and indirect effects (through SHP), contributes to repression of bile acid synthesis and bile acid uptake and the induction of canalicular and alternative basolateral bile acid excretion. These effects minimize bile acid and cholephilic accumulation inside the hepatocyte and results in an increase in bile flow. Induction of bile acid detoxification also occurs through induction of enzymes such as CYP3A4, SULT2A1, UGT2B4, and UGT2B7.
PXR (Pregnane-X-receptor, NR1I2)	Intracellular xenobiotic sensor	PXR is activated by a wide variety of endobiotics, xenobiotics and secondary hydrophobic bile acids (lithocholic acid). Its activation results in transactivation of a set of target genes leading to induction of phase I and II bile acid and bilirubin detoxification systems as well as to the induction of canalicular and alternative basolateral bile acid excretion.
CAR (constitutive androstane receptor, NR1I3)	Intracellular xenobiotic sensor	Induction of endobiotic, xenobiotic, bile acid and bilirubin detoxification systems.
SHP (short heterodimer partner, NR0B2)	FXR target	Upon activation by FXR, SHP represses bile acid synthesis and also hepatic and intestinal bile acid uptake
HNF4α (Hepatocyte Nuclear Factor 4 α , NR2A1)	Constitutive transactivator	HNF4 α is required for constitutive expression of several basolateral uptake systems and indirectly regulates PXR, CAR and HNF1 α target genes.
VDR Vitamin D receptor (NR1I1)	Ligand of lithocholic acid in liver and intestinal cells	Induction of bile acid detoxification systems and alternative basolateral bile acid excretion. Induction of biliary and intestinal bile acid reabsorption

* See abbreviations list at the beginning of the article.

Members of the nuclear receptor superfamily are mentioned by their common name followed by the official name (as proposed by the Nuclear Receptors Nomenclature Committee *Cell* 1999;97:161–163) in brackets

Table 2

Summary of experimental and clinical data on the role of selected nuclear receptors in Non-alcoholic fatty liver disease^{*,#}.

NR member	Main function	Metabolic effects of activation/deactivation relevant for NAFLD
PPARs (peroxisome proliferator-activated receptor)	Lipid-activated transcriptional regulators of metabolism and inflammation	<p>PPARα (NR1C1): reduced activation leading to decreased beta oxidation of fatty acids contributes to steatosis. Activation with synthetic ligands (fibrates) abolishes steatosis and reduce fatty liver in rodents but is ineffective in humans.</p> <p>PPARγ (NR1C3): mainly expressed in adipose tissue in normal conditions. Overexpressed in steatotic livers. Pharmacological activation with synthetic ligands ameliorates insulin resistance in rodents and humans and possesses anti-inflammatory effects through an increased secretion of adiponectin. Pioglitazone and rosiglitazone has been tested in clinical trials with promising results in patients with NASH. Main side effect is weight gain. No long-term follow-up is available.</p> <p>PPARδ (NR1C2): its activation reduces fat burden and protect against lipotoxicity caused by ectopic lipid deposition. Specific ligands not yet available for clinical testing.</p>
PXR (Pregnane X receptor, NR1I2) and CAR (constitutive androstane receptor, NR1I3)	Intracellular xenobiotic sensors	<p>PXR and CAR promote hepatic lipid storage due to decreased hepatic fatty acid β-oxidation.</p> <p>PXR mediates a SREBP-independent lipogenic pathway by activating the free fatty acid uptake transporter CD36.</p> <p>CAR regulates serum triglyceride levels under conditions of metabolic/nutritional stress.</p> <p>Although CAR null mice is somewhat protected of steatosis, experimental data on the effects of CAR agonist in NASH is conflicting.</p>
FXR (farnesoid X receptor, NR1H4)	Intracellular bile acid sensor	<p>FXR activation regulates lipid (inhibits TG synthesis) and glucose metabolism (inhibits gluconeogenesis) through the FXR-SHP regulatory cascade.</p> <p>The synthetic FXR agonist WAY-362450 reduces inflammatory cell infiltration, aminotransferase levels and markers of hepatic fibrosis in experimental NASH.</p> <p>Another synthetic FXR agonist 6α-ethyl-chenodeoxycholic acid, [6E-CDCA] prevents body weight gain as well as liver and muscle fat accumulation and ameliorates insulin resistance and reduces lipogenic program in obese rats.</p> <p>A phase 2 clinical trial assessing the effects of 6E-CDCA in human NASH is ongoing.</p>

* See abbreviations list at the beginning of the article.

Members of the nuclear receptor superfamily are mentioned by their common name followed by the official name (as proposed by the Nuclear Receptors Nomenclature Committee *Cell* 1999;97:161–163) in brackets