Published in final edited form as:

Exp Biol Med (Maywood). 2010 May ; 235(5): 547–560. doi:10.1258/ebm.2009.009249.

Pathogenesis of alcoholic liver disease: the role of nuclear receptors

Maxwell Afari Gyamfi and Yu-Jui Yvonne Wan

Department of Pharmacology, Toxicology, and Therapeutics, University of Kansas Medical Center, 3901 Rainbow Blvd, Kansas City, Kansas 66160-7417, USA

Abstract

Ethanol consumption causes fatty liver, which can lead to inflammation, fibrosis, cirrhosis and even liver cancer. The molecular mechanisms by which ethanol exerts its damaging effects are extensively studied, but not fully understood. It is now evident that nuclear receptors (NRs), including retinoid x receptor α and peroxisome proliferator-activated receptors, play key roles in the regulation of lipid homeostasis and inflammation during the pathogenesis of alcoholic liver disease (ALD). Given their pivotal roles in physiological processes, NRs represent potential therapeutic targets for the treatment and prevention of numerous metabolic and lipid-related diseases including ALD. This review summarizes the factors that contribute to ALD and the molecular mechanisms of ALD with a focus on the role of NRs.

Keywords

nuclear receptors; alcoholic liver disease; retinoid x receptor alpha; peroxisome proliferator-activated receptors; ethanol; lipogenic transcription factors

Introduction

Alcoholic liver disease (ALD) is damage to the liver and its function due to alcohol abuse and usually occurs after years of excessive drinking. Changes in the liver include fatty liver, inflammation and cirrhosis.^{1–3} Moreover, chronic alcohol consumption is an established risk factor for the development of hepatocellular carcinoma in patients with liver cirrhosis.^{4,5} ALD may occur in patients who consume excessive amounts of alcohol. Reports indicate that the risk of developing liver damage depends on the amount of alcohol consumed.^{6–8} Evidence suggests that daily ethanol consumption exceeding 40–80 g/d for men and 20–40 g/d for women for 10–12 y may lead to ALD.^{1,9,10} Alcohol use remains the most common cause of liver-related mortality and a major cause of death and disability worldwide.¹¹ Since the 1970s, there has been a gradual decline in ALD mortality in many countries.⁹ However, current reports indicate that the incidence of ALD and subsequent deaths is on the rise.⁹ In the United States, the mortality rate for ALD in 1993 was 7.9 per 100,000, while in 2000 it had risen to 9.6 per 100,000.^{12,13}

Although a clear correlation exists between cumulative alcohol intake and liver disease, only some alcohol drinkers develop signs of ethanol-induced liver damage. It is now clear that individuals differ in their susceptibility to ALD. The susceptibility of individuals to the toxic effects of alcohol consumption may involve complex interactions between genes and the

environment. To date, genes encoding the principal alcohol-metabolizing enzymes, alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH), are the only genes that have been firmly linked to vulnerability to alcoholism and possible risk for ALD.^{14–18} Other factors that affect susceptibility to ALD include the amount of alcohol ingested over time, ethnicity, female gender, adolescent age, drinking multiple varieties of alcohol, drinking alcohol in-between meals, poor nutrition, obesity, hepatitis C virus infection and polymorphisms in genes (cytochrome P450 2E1 [CYP2E1], glutathione *S* transferases [GSTs] and tumor necrosis factor- α [TNF- α]).^{6,9,14,19–26} Epidemiological data indicate that some minority groups suffer more severe adverse effects from alcohol consumption.²⁷ It has been suggested that some of these consequences may be due to special characteristics of these minority populations, including nutrition, socioeconomic status, hygiene, health-care delivery or other environmental conditions.²⁸ In addition, reports indicate that polymorphisms in several genes, including ADH and ALDH observed among Asians, African-Americans and Caucasians, may be an important biological factor contributing to differences in cell and tissue damage, intolerance to alcohol or both observed in these groups.^{14,29–31} Among the various ethnic groups, Hispanic and African-American men have the highest risk of alcoholism.^{15–17,32}

Ethanol produces a wide spectrum of hepatic injuries in humans and experimental animals, the most characteristic being interference in lipid metabolism. Hepatic lipid homeostasis is maintained by balanced lipid synthesis, catabolism (β -oxidation) and secretion. Alcohol metabolism changes the redox state of the liver, which leads to alterations in hepatic lipid, carbohydrate, protein, lactate and uric acid metabolism. The molecular mechanisms, which account for these alterations, are not completely understood. A large body of evidence implicates the involvement of ligand-activated transcription factors called nuclear receptors (NRs) in alcohol-induced liver injury. These NRs play diverse roles in cellular processes and are receptors for fatty acids, cholesterol, oxysterols and xenobiotics generated after ethanol ingestion. This review, however, will mainly focus on those NRs that are central to the pathogenesis of ALD and their role in orchestrating the complex transcriptional programs that govern lipid and inflammatory homeo-stasis in ALD.

Ethanol metabolism

Ethanol is metabolized predominantly in the liver via two well-characterized pathways.^{18,33,34} The first involves ADH, an NAD⁺-dependent enzyme located in the hepatic cytosol, which catalyzes the conversion of ethanol to acetaldehyde, a potent toxicant that accounts for the most toxic effects of ethanol.³³ Acetaldehyde produced from ethanol is further converted to the non-toxic acetate by a mitochondrial ALDH.³⁴ Both steps are coupled with the reduction of NAD⁺ to NADH. The increased NADH/ NAD⁺ ratio affects the metabolism of carbohydrates and lipids in cytoplasm and mitochondria. This leads to impaired gluconeogenesis and diminished substrate flow through the citric acid cycle, with acetyl CoA diverted to fatty acid synthesis. The NADH-induced inhibition of mitochondrial fatty acid β -oxidation, combined with increased fatty acid synthesis, contributes to the pathogenesis of fatty liver, the initial stage of ALD.^{35–38}

Evidence indicates that, rather than being an epiphenomenon of excessive alcohol intake, steatosis could play a direct role in progression to more advanced disease.³⁹ It is now clear that the severity and pattern of steatosis in ALD predicts the subsequent risk of fibrosis and cirrhosis. The current model of pathogenesis from healthy liver to alcohol-induced liver injury suggests a two-hit progression with steatosis being considered as the ‘first hit’. Cellular insults such as oxidative stress, lipid peroxidation, direct lipid toxicity, mitochondrial dysfunction and/or infection causing hepatic inflammation can be the second hit, which lead to alcoholic steatohepatitis.³ Besides ADH, another enzyme that affects

ethanol action is CYP2E1, a microsomal enzyme that metabolizes ethanol at high concentrations and also metabolizes vitamin A, acetaminophen and protease inhibitors.^{18,40,41} CYP2E1 activity is induced 2–10-fold after chronic ethanol exposure and has been implicated as the source of oxidative stress.⁴²

Oxidative and inflammatory factors influencing ALD

Several pathways or factors, which are known to be involved in the pathogenesis of ALD, are summarized below. Ethanol consumption predominantly results in a decrease in the hepatocyte level of *S*-adenosylmethionine (SAME) and increases in two toxic metabolites, homocysteine and *S*-adenosylhomocysteine (SAH).^{43–50} Furthermore, alcohol causes a shift in the expression of methionine adenosyltransferase (MAT) genes in the liver from MAT1A to MAT2A, which correlates with decreased SAME levels.^{49,50} Chronic ethanol consumption markedly inhibits methionine synthase activity resulting in the depletion of SAME.⁵¹ Ethanol-induced upregulation of betaine-homocysteine methyltransferase (BHMT) or betaine supplementation can transiently cause elevations in SAME levels.^{51,52} Decreased SAME levels are associated with decreased antioxidant defense, fibrogenesis, induction of TNF- α and increased DNA strand breaks, all of which lead to liver injury.⁵⁰ An association of ethanol-induced hyperhomocysteinemia and endoplasmic reticulum (ER) stress has also been proposed to be important in the observed alcoholic fatty liver, necroinflammation and apoptosis seen after alcohol exposure.^{53,54} Recent studies have shown that osteopontin, a matricellular protein, also plays a significant role in ALD.⁵⁵ Elevated osteopontin levels correlated with neutrophil infiltration and liver injury.⁵⁶ The gender difference in the susceptibility of mice to alcohol-induced liver injury may be due to higher hepatobiliary expression of osteopontin in females than males.⁵⁶ Plasminogen activator inhibitor-1 (PAI-1), which inhibits fibrin degradation and mediates inflammatory signaling, is also implicated in alcohol-induced liver injury.^{57–59} PAI-1 levels were increased in response to acute and chronic ethanol intake in mice.⁵⁹ Additionally, ethanol-induced steatosis and lipid peroxidation is blocked when PAI-1 is absent or low.⁵⁹ Reports indicate that PAI-1 mRNA and protein are significantly increased in osteopontin $-/-$ mice, suggesting that osteopontin can suppress PAI-1 expression.^{60,61}

The complement pathway, an important component of the innate and adaptive immune response, is involved in the pathogenesis of ALD.⁶² The proteins and glyco-proteins, which constitute the complement system, are synthesized by the liver hepatocytes, macrophages and other types of cells. The expression of C1, C2, C3, C8 and C9, which are involved in the activation of classical and alternative complement pathways, is induced in alcohol-induced fatty liver.^{63–67} Reports indicate that C3 and C5 differentially contribute to the pathogenesis of ethanol-induced liver injury.⁶⁷ Ethanol-fed C3-deficient mice did not develop hepatic steatosis, but still had liver injury, as well as increased expression of inflammatory cytokines in the liver.⁶⁷ In contrast, ethanol-fed C5-deficient mice developed hepatic steatosis, but were completely protected from ethanol-induced liver injury and increases in inflammatory cytokines.⁶⁷ Interleukins (ILs) have also been shown to play a role in ethanol-induced liver injury. IL-6-deficient mice are more prone to ethanol-induced apoptosis and liver injury.⁶⁸ IL-6 exerts its protective effect via an increase in hepatocyte proliferation, induction of antiapoptotic factors, peroxisome proliferator-activated receptors α (PPAR α) activity and a reduction in steatosis.^{68,69} Reports indicate that nuclear factor erythroid 2-related factor 2 (Nrf2) is induced in ethanol-fed mouse liver, suggesting a protective role of Nrf2 against alcohol-induced liver damage.⁷⁰ Nrf2-null mice exhibit impaired detoxification of acetaldehyde and increased sensitivity to alcohol-induced liver injury.⁷¹

The above pathways involving oxidative stress, antioxidant molecular synthesis, ER stress and inflammation illustrate the complexity of ethanol-induced tissue injury.

Endocrine and metabolic factors influencing ALD

Reports indicate that low levels of adiponectin, an important antisteatotic and anti-inflammatory cytokine produced by adipocytes, may also contribute to steatosis and inflammation in ALD.^{72–76} Chronic ethanol administration decreases plasma adiponectin levels as well as hepatic adiponectin receptor-1 (AdipoR1) mRNA levels, leading to steatosis.^{75,77} Adiponectin attenuates alcoholic fatty liver by up-regulating PPAR α , PPAR γ coactivator-1 α (PGC-1 α) and carnitine palmitoyl transferase-1. In addition, adiponectin down-regulates acetyl-CoA carboxylase (ACC)¹⁹ and fatty acid synthase (FAS), key enzymes involved in fat biosynthesis.^{75,78–82} Adiponectin also has anti-inflammatory effects. The administration of adiponectin reduces TNF- α levels in ethanol-fed mice.⁷⁵ The action of adiponectin is mediated in part by increase in AMP-activated protein kinase (AMPK) activity.^{79,82} It has been proposed that AMPK acts as a metabolic master switch and its activation leads to a concomitant inhibition of energy-consuming bio-synthetic pathways, such as FAS.⁸³ AMPK activation inhibits ACC activity directly by phosphorylation, and inhibits ACC expression indirectly via the suppression of sterol regulatory element-binding protein-1c (SREBP-1c), a key lipogenic transcription factor.^{84,85} SREBP-1 activity is regulated by reversible acetylation at specific lysine residues.⁸⁶ Findings have demonstrated that sirtuin 1 (SIRT-1), a NAD⁺-dependent class III protein deacetylase that regulates lipid metabolism, is involved in ALD.⁸⁷ SIRT-1 is known to bind to SREBP-1, resulting in its inactivation via deacetylation. Ethanol exposure reduced the level of SIRT-1 content blocking the SIRT-1-induced deacetylation of SREBP-1.⁸⁷ In addition, ethanol-induced transcription of SREBP-1-regulated genes was suppressed by an SIRT-1 agonist, resveratrol.⁸⁸ Hepatic SIRT-1 knock down in mice induces the expression of SREBP-1c and its target genes encoding lipid-synthesizing enzymes.⁸⁹ Adipose tissues in ethanol-fed rats also express more leptin, a TNF- α -inducible mRNA.⁹⁰ Thus, these targeted effects of ethanol on the adipose tissue play important roles in the development of steatosis and inflammation.

Animal models of ALD

Animal models are valuable in elucidating the molecular mechanisms involved in ALD. Two frequently used animal models are the Lieber–DeCarli liquid diet and the Tsukamoto–French intragastric tubing feeding model.^{91–94} The Lieber–DeCarli liquid diet model provides an excellent means to reproduce the early stages of ALD, including liver injury, steatosis and oxidative stress as well as studying the relative roles of alcohol, lipids and therapeutic agents. Rodents fed the Lieber–DeCarli diet reduce their overall food intake; therefore, pair-fed control animals are mandatory to interpret the experimental results. After determining the caloric intake of the ethanol-treated animal, the exact amount of calories is given to the pair-fed control animal on the next day. Tsukamoto and French developed continuous enteral–ethanol administration via intragastric infusion.^{94–96} After laparotomy, a catheter is implanted intragastrically facilitating a continuous infusion of ethanol up to 16.5 g/kg/d. Thus, very high blood-alcohol levels can be achieved. The Tsukamoto–French model produces pathological changes, which resemble human ALD, including microvesicular and macrovesicular fat, megamitochondria, apoptosis, central lobular and pericellular fibrosis, portal fibrosis, bridging fibrosis, central necrosis and infiltrating inflammatory leukocytes as well as lymphocytes.^{91,97}

The dietary fat content and composition are principal determinants of the degree of fatty infiltration in animals and humans ingesting alcohol.^{98–100} In ethanol-fed rats, robust levels of hepatic triglycerides accumulate when fat content increases above 25% of the calories in the diet.⁹⁸ Ethanol with low fat diet (5% of the calories) does not produce fatty liver or evidence of lipid peroxidation unless a high blood-alcohol level is achieved by the

intra-gastric infusion model.^{95,101} Studies using the Lieber–DeCarli liquid diet or the intra-gastric ethanol-fed animal model have demonstrated that diets enriched in saturated fatty acids or medium-chain triglycerides protect against alcohol-induced liver injury. However, diets containing polyunsaturated fatty acids promote liver injury.^{82,100,102–105} The administration of saturated fat reversed alcohol-induced liver injury in rats and improved liver pathological changes despite continued ethanol administration.^{106,107} Another model that has been used to study the acute ethanol effects on the liver is gastric intubation or intraperitoneal injection in rodents. The binge model originally described by Carson and Pruett was designed to achieve blood-alcohol levels, behavioral effects and physiological changes comparable to those seen in human binge drinking.¹⁰⁸ The dose of alcohol used to mimic human binge drinking in rodents is 4–6 g/kg body weight.^{109–111} Binge drinking is the most common pattern of alcohol consumption in school-age youth. The probability of becoming a chronic drinker at an adult age was higher in male and female adolescent binge drinkers than in non-bingers.^{112,113} While binge animal models may not completely mimic liver injury in humans, reports indicate a significant contribution of binge drinking to the incidence of cirrhosis seen in patients with ALD.^{114–116}

By taking advantage of genetically manipulated animals, the role of specific genes in the development of ALD has been elucidated. Examples of mouse gene knockouts (KO) include: PPAR α , retinoid x receptor (RXR α), SREBP-1c, BHMT-transgenic, CYP2E1, CYP2E1-transgenic, tumor necrosis receptor I (TNF-RI), TNF-RII, NADPH oxidase, cell surface receptor CD14, toll-like receptor 4, intracellular adhesion molecule-1, PAI-1, IL-6, Nrf2 and osteopontin mice.^{44,47,71,117–121} The reader is referred to the following references for a discussion of gene-altered mouse models and their impact on the pathophysiology of ALD.^{44,46,47,59,117,120–124} This review focuses on the role of NRs on the pathophysiology of ALD.

Nuclear receptors

NRs are transcription factors that regulate diverse processes, including reproduction, embryonic development, cell differentiation and cellular homeostasis.^{125,126} NRs are expressed differentially among tissues, and are comprised of at least 49 members, some of which in a circadian manner.¹²⁷ Most NRs are composed of four independent but interacting functional modules.^{125,128} At the amino-terminus, there is a poorly conserved region called activation function 1, which is responsible for ligand-independent transcriptional activation and is involved in the coordinated interaction of co-activators and co-repressors. Immediately adjacent to activation function 1, there is a highly conserved DNA-binding domain, which contains two zinc-finger motifs, responsible for high-affinity recognition and binding to the canonical DNA hexamer sequences comprising the specific response elements. A small hinge region facilitates the three-dimensional functional organization of the multiple domains. The ligand-binding domain serves the greatest differentiating and identifying function among NRs family members, determining the affinity of receptors for various potential ligands, and is responsible for the species specificity of ligand responsiveness. The C-terminus region, activation function 2, provides ligand-dependent activation, via a complex three-dimensional conformational switch to coordinate interactions with co-regulators.^{125,129} However, there are exceptions, for example, a small heterodimer partner lacks a DNA-binding domain and yet heterodimerizes with other NRs often in a ligand-dependent manner.^{42,130,131}

The NR family is classified into three groups:¹²⁵ steroid hormone receptors, adopted orphan NRs and orphan NRs.¹ NRs that generally bind DNA as homodimers and are activated with high-affinity by steroid hormones are the steroid hormone receptors. Members of this group include the receptor for glucocorticoids, mineralocorticoid, estrogen, androgen and

progesterone.² The adopted orphan NRs function as heterodimers with RXRs. These orphan receptors are considered adopted, as studies show that they can bind physiological ligands and display physiological effects. Members of this group include the receptors for fatty acids (PPARs), bile acids (farnesoid x receptor [FXR]), oxysterols (liver x receptor [LXR]), xenobiotics (pregnane x receptor [PXR] and constitutive androstane receptor [CAR]) and retinoic acids (retinoic acid receptor).³ The orphan NRs refer to transcription factors speculated to be NRs based on gene/protein structure, for which no specific ligands have yet been identified, or which appear to lack a functional ligand-binding domain based on structural analysis. Members of this group include nerve growth factor-induced clone B, NR related 1, neuron-derived orphan receptor 1, small heterodimer partner, liver-related homologue 1 and hepatocyte nuclear factor 4 α (HNF4 α).¹²⁵ Different NRs bind to their response elements as homodimers, as heterodimers with RXRs, or as monomers. Binding of ligand to the ligand-binding domain elicits a series of sequential reactions, including conformational changes in the receptors, release of the co-repressor complex and recruitment of co-activators.^{128,132} Consequently, the activated NR induces target gene expression. In this way, NRs mediate chemical signals into transcriptional activation of a network of target genes.

NRs and ALD

A number of NRs are important in the pathogenesis of ALD because they act as intracellular sensors of free fatty acids and cholesterol metabolites as well as being involved in inflammatory and xenobiotic signaling. Among them, the role of RXR α and PPARs in ALD has been studied most extensively.

RXR

RXRs (α , β and γ) utilize 9-*cis* retinoic acid as a high-affinity ligand.^{133,134} RXRs regulate fundamental biological processes including reproduction, cell differentiation, bone development, hematopoiesis and pattern formation during embryogenesis.¹²⁸ Gene KO studies have been conducted on all three RXR genes. Mice missing RXR β or RXR γ are viable.^{135,136} However, RXR α -KO mice are not viable due to defects in cardiac development.^{135,137,138} This phenotype was also observed in the embryonic vitamin A deficiency syndrome, suggesting a critical role for RXR α in the vitamin A signaling pathway. Among the RXR isoforms, RXR α is the most highly expressed in the liver.^{134,139} To address the role of RXR α in the liver physiology of adult mice, a *cre/lox*-mediated recombination was used to mutate selectively the RXR α gene in adult hepatocytes, by deleting the fourth exon encoding for the majority of the of the RXR α protein.¹⁴⁰ The examined pathways involving class II NRs, such as fatty acid, cholesterol, carbohydrate and xenobiotic metabolic pathways mediated by RXR α are compromised due to hepatocyte RXR α deficiency.^{140–143}

RXR α and ethanol metabolism

Ethanol and retinol (vitamin A) share the hydroxyl moiety and are metabolized by common enzymes, ADHs and ALDHs.^{144–146} A similar two-step process is involved in the metabolism of both alcohol and retinol, such that the two processes are in competitive inhibition with each other.^{144,147} Both alcohol and retinol are first oxidized to the aldehyde form, and aldehyde is subsequently oxidized to the acid form.^{148,149} The hepatic levels of vitamin A, retinoic acid and RXR α are decreased by alcohol administration.^{150,151} Reduced serum and hepatic vitamin A concentrations have been found in chronic alcoholics.¹⁵² Thus, reduction in retinoid signaling is implicated in ALD.^{144,148,150,153} Although retinoic acid has been shown to be centrally involved in the pathogenesis of ALD, the mechanism and nature of such influences have remained largely unknown.

To understand the role of RXR α in alcohol detoxification and ALD, the effect of hepatocyte RXR α deficiency on the expression of alcohol-metabolizing enzymes was analyzed in hepatocyte RXR α -deficient (hepatocyte RXR α -KO) mice.¹²³ Hepatocyte RXR α deficiency resulted in a significant increase in hepatic ADH activity and ADH1 protein, but not ADH2 and ADH3 enzyme activities.¹²³ Moreover, the levels of ADH1, ADH2, ADH3 and ADH4 mRNAs in the livers were not different between the mutant and wild-type mice.¹²³ In human liver, mitochondrial (low K_m) ALDH2 oxidizes most of the ethanol-derived acetaldehyde; however, in rodents both mitochondrial and cytosolic ALDH isozymes are important in acetaldehyde oxidation.¹⁵⁴ The activities of mitochondrial ALDH2 and cytosolic ALDH are reduced when hepatocyte RXR α is knocked out.¹²³ Kinetic analysis revealed that the cytosolic high-affinity ALDH1 with high acetaldehyde-oxidizing capacity is more impacted than other ALDH isoforms with RXR α deficiency. Consistent with the decreased cytosolic ALDH1 activity, both ALDH1A1 protein and mRNA levels were significantly reduced in hepatocyte RXR α -KO mouse livers. Accordingly, after a single dose of intragastric administration of ethanol, the blood ethanol levels in the hepatocyte RXR α -KO mice were significantly lower in comparison with that in wild-type mice. Furthermore, hepatic acetaldehyde clearance was slower in hepatocyte RXR α -KO mice than in wild-type mice.¹²³ These findings provide *in vivo* evidence that the level of *ADH1* expression regulated by RXR α is an important factor in determining the rate of ethanol elimination and influences the risk for alcohol-induced liver injury. The effect of hepatocyte RXR α on ethanol metabolism is summarized in Figure 1.

Both the Tsukamoto–French intragastric tubing alcohol feeding and the Lieber–DeCarli ethanol models were used to study the impact of hepatocyte RXR α on ALD.^{44,46} The histological score (fat/necrosis/inflammation/fibrosis) was significantly higher in alcohol-fed hepatocyte RXR α -KO than in wild-type mice. Furthermore, compared with wild-type mice, hepatocyte RXR α -KO mice had significantly lower levels of S-AE and glutathione, which were further reduced after alcohol treatment.⁴⁴ Glutamate-cysteine ligase catalytic subunit, glutathione *S*-transferase- μ and glutathione peroxidase (Gpx) 1 gene and protein expression or enzyme activities are down-regulated in the livers of hepatocyte RXR α -KO mice.^{155,156}

RXR α and lipid homeostasis

To dissect the role of RXR α in lipid homeostasis during ethanol-induced liver injury, wild-type and hepatocyte RXR α -KO mice were fed ethanol-containing diets or pair-fed control diets for six weeks using the Lieber–DeCarli ethanol model.⁴⁶ Liver injury was found in hepatocyte RXR α -KO mice, but not in the wild-type mice.⁴⁶ Steatosis induced by ethanol was more pronounced in hepatocyte RXR α -KO mice than in wild-type mice in the intragastric ethanol infusion model.⁴⁴ Furthermore, ethanol-induced hepatic free fatty acids and cholesterol levels were higher in hepatocyte RXR α -KO than wild-type mice.⁴⁶ Basal hepatic liver fatty acid-binding protein (L-FABP) level was reduced with RXR α deficiency.^{46,140,157} Ethanol induces L-FABP to provide protection against hepatic free fatty acid toxicity in wild-type mice; however, this protective effect is absent with RXR α deficiency.⁴⁶ Furthermore, hepatocyte RXR α -KO mice are more sensitive to the development of steatohepatitis when fed a methionine-choline-deficient (MCD) diet.¹⁵⁷ MCD diet ingestion induces the expression of the SREBP-regulated genes (FAS, ACC-1 α and HMG CoA reductase), which in turn increases hepatic lipids and bile acid synthesis.¹⁵⁷ In hepatocyte RXR α -KO mice, the PPAR α -mediated fatty acid β -oxidation is compromised, which leads to hepatic fatty acid overload.¹⁵⁷

RXR α and inflammation

RXR α and other NRs play important roles in the inflammatory process.¹⁵⁸ For example, TNF α and IL-1 can decrease the expression of RXR α , PPAR α , PPAR γ , LXR α and their co-

factors in human hepatoma Hep3B cells.¹⁵⁹ The LPS-induced acute phase response is associated with decreased hepatic proteins involved in lipid metabolism concomitant with the reduction of hepatic RXR α level in mouse and hamster.^{160–162} The down-regulation of RXR α in inflamed liver is due to nuclear export and degradation.^{160,162} The RXR α -mediated pathways could also be inhibited due to direct interaction between nuclear factor- κ B (NF- κ B) p65 and the RXR α DNA-binding domain and thus may prevent the binding of RXR α to consensus DNA sequences.¹⁶³ These findings clearly demonstrate a down-regulation of RXR α signaling during the inflammatory process. Furthermore, RA inhibits hepatic macrophage TNF- α expression and is known to have anti-inflammatory effects.¹⁵¹ LG268, which is an RXR-specific ligand, inhibits TNF- α mRNA expression.¹⁵¹ Although the anti-inflammatory action of RA was found to involve destabilization of the TNF- α mRNA, it also could possibly involve RXR α .¹⁵¹

The anti-inflammatory role of RXR α has been demonstrated using ethanol-fed wild-type and hepatocyte RXR α -KO mice.⁴⁶ NF- κ B regulates the expression of a variety of genes involved in alcohol-induced liver injury.^{164–167} Ethanol increases NF- κ B p65-binding activity in hepatocyte RXR α -KO mouse liver, but not in wild-type mouse liver.⁴⁶ The activation of NF- κ B should increase the expression of NF- κ B-regulated cytokines and chemokines in hepatocyte RXR α -KO mice.⁴⁶ Accordingly, TNF- α , IL-6 and IL-1 β mRNA levels are much higher in ethanol-fed hepatocyte RXR α -KO mice than in ethanol-fed wild-type mice.⁴⁶

In response to cytokines or growth factors, the signal transducer and activator of transduction 3 (STAT3) is activated. Activated STAT3 regulates the expression of genes that play key roles in proliferation and inhibition of apoptosis.^{168,169} IL-6 is readily detected in patients with ALD, and its concentration correlates positively with the extent of the disease.¹⁷⁰ Furthermore, IL-6-deficient mice are more prone to ethanol-induced apoptosis in the liver.⁶⁸ The activation of STAT3 is decreased in ALD patients with cirrhosis.¹⁷¹ Although IL-6 mRNA and protein levels were induced in ethanol-fed hepatocyte RXR α -KO mice, elevated IL-6 did not result in STAT3 activation.⁴⁶ Consistent with this observation, although ethanol induced the expression of anti-apoptotic protein Bcl-xL, a direct STAT3 target gene, in wild-type mice, no increase was found in ethanol-fed hepatocyte RXR α -KO mice.⁴⁶ Furthermore, ethanol-mediated reduction of Bcl-2 was greater in hepatocyte RXR α -KO than wild-type mice.⁴⁶ Further investigation is needed to explain the different effects of ethanol on Bcl-xL and Bcl-2 expression.⁴⁶ Similar to our report, the differential effect of ethanol on Bcl-xL and Bcl-2 expression has also been found.¹⁷² In agreement, apoptotic cells were found in ethanol-fed hepatocyte RXR α -KO mice, but were not noted in ethanol-fed wild-type mice.⁴⁶ Similarly, MCD diet-induced proinflammatory gene expressions are higher in hepatocyte RXR α -KO mice than in wild-type mice.¹⁵⁷

PPAR α

PPAR α is responsible for peroxisome proliferation. It also regulates lipid metabolism and transport, fatty acid oxidation and glucose homeostasis.¹⁷³ PPAR α is predominantly expressed in cells or tissues capable of oxidizing fatty acids, such as hepatocytes, heart, muscle, brown adipose tissue and the kidney. PPAR α can be activated by natural lipophilic ligands, such as fatty acids and their derivatives, certain leukotriene products and drugs such as non-steroidal anti-inflammatory drugs and fibrates.^{174,175} The absence of PPAR α expression in KO mice prevents the induction of several hepatic PPAR α target genes including acyl-CoA oxidase (ACOX) by peroxisome proliferators.^{174,175} There is significant species difference in PPAR α expression; human livers express less than 1/10th the level of PPAR α mRNA and functional DNA-binding capacity compared with mouse livers.¹⁷⁶ This difference might explain why rodents are more susceptible to the toxic and carcinogenic

effects of peroxisome proliferators.¹⁷⁶ PPAR α target genes are those that encode fatty acid transporters, proteins involved in export (apolipoprotein [Apo] B), the microsomal triglyceride transfer protein, L-FABP and acyl-CoA dehydrogenase.¹⁷³ The activation of these genes results in increased uptake and oxidation of free fatty acids, increased triglyceride hydrolysis and up-regulation of ApoA-I and -II. The net effect is increased fatty acid oxidation, decreased serum tri-glycerides, a rise in high-density lipoprotein and an increase in cholesterol efflux. The relationship between PPAR α and fatty liver became evident when steatosis was observed in aged PPAR α KO mice.¹⁷⁷ Starvation activates PPAR α .^{178,179} PPAR α KO mice exhibit steatosis, myocardial lipid accumulation and hypoglycemia during short-term starvation or after high fat diet administration.^{178,179}

PPAR α is a circadian gene.^{180,181} The diurnal variation of lipogenic and cholesterologenic gene expression was attenuated or abolished in PPAR α KO mice suggesting the importance of PPAR α as a mediator for the circadian regulation of lipid metabolism.^{182,183} Both acute and chronic alcohol intake can affect many aspects of circadian rhythms, including physiological, endocrine and behavioral functions. However, the effect of central and peripheral circadian rhythms involved in alcohol-induced liver injury remains to be addressed.

The role of PPAR α in ALD has been demonstrated with the PPAR α KO mice.¹²⁰ Ethanol-fed PPAR α -null mice have hepatocyte damage, which is not found in wild-type mice. Down-regulation of PPAR α activity and fatty liver was observed following intragastric ethanol infusion of rats.^{184,185} Treatment of ethanol-fed animals with PPAR α agonists reduces the toxic effects of ethanol and reverses hepatic fat accumulation.^{119,150,184} Fish oil contains *n*-3 fatty acids, which are PPAR α activators. Feeding mice fish oil prior to ethanol administration prevents acute ethanol-induced fatty liver.¹⁸⁶ IL-6 treatment ameliorates alcoholic fatty liver, which is in part attributed to the up-regulation of PPAR α and increased mitochondrial β oxidation of fatty acids.⁶⁹ These results support the importance of PPAR α in preventing alcohol-induced fatty liver and injury. However, activation of PPAR α using fibrates also causes cholestasis in humans and mice and other undesired effects such as hepatomegaly in rodents.^{187–191} Furthermore, ethanol-fed PPAR α KO mice have lower levels of GPx, superoxide dismutase and catalase, as well as increased lipid peroxides compared with wild-type controls.¹²⁰

The role of PPAR α in alcoholic fatty liver has also been studied in cultured hepatocytes. Ethanol exposure of H4IIEC3 rat hepatoma cells expressing alcohol-metabolizing enzymes causes reduced binding by the RXR/PPAR α to a PPAR α binding site located on the ACOX promoter.¹⁹² This effect of ethanol is enhanced by the ALDH inhibitor cyanamide and is abolished by the ADH inhibitor, 4-methylpyrazole implicating the involvement of acetaldehyde.¹⁹³

PPAR α and inflammation

The role of PPAR α in inflammation was first observed using PPAR α KO mice.¹⁹⁴ In mice lacking the PPAR α gene, the response to topical inflammatory mediator leukotriene B₄ or arachidonic acid, but not phorbol ester 12-*O*-tetradecanoylphorbol-13-acetate, is prolonged compared with the response in wild-type mice.¹⁹⁴ Furthermore, dietary administration of (*n*-3) polyunsaturated fatty acids results in increased survival of the animals when they are challenged with bacteria or endo-toxin.^{195,196} Fish oil has been found to decrease circulating levels of proinflammatory cytokines (TNF- α , IL-6, IL-1) in patients with endotoxemia.¹⁹⁵ PPAR α is able to inhibit inflammatory responses by interfering with NF- κ B and activator protein 1 activation through a direct protein-protein interaction with p65 or c-Jun, respectively.^{197,198} PPAR α is also able to increase inhibitory κ B (I κ B)- α leading to the prevention of p50- or p65-NF- κ B nuclear translocation.^{120,199,200} This action leads to the

repression of cytokines, cell adhesion molecules and proinflammatory molecules such as inducible nitric oxide synthase (iNOS) and C-reactive protein. The activation of p65-NF- κ B was significantly greater in hepatic nuclear fractions from ethanol-fed PPAR α KO mice compared with ethanol-fed wild-type mice.¹²⁰

PPAR γ

PPAR γ is highly expressed in adipocytes, hematopoietic cells and hepatic stellate cells, and to a lesser extent in pancreatic β cells, spleen, skeletal muscle, macrophages and intestinal cells.²⁰¹ Hepatocytes express very low levels of PPAR γ . PPAR γ is involved in adipocyte differentiation, glucose metabolism and lipid storage.²⁰² Reports indicate that PPAR γ ligands can inhibit inflammatory responses by decreasing IL-6, TNF- α , IL-1 β secretion and iNOS production in macrophages and Kupffer cells. PPAR $\gamma^{+/-}$ mice have increased susceptibility to experimentally induced arthritis and inflammatory bowel disease.²⁰³ The anti-inflammatory mechanisms mediated by PPAR γ involve nuclear export of RelA (p65), thereby preventing NF- κ B-induced proinflammatory gene activation.^{204,205}

The composition of PPAR isoforms might change in fatty livers. Leptin, which can inhibit appetite, is a peptide hormone produced predominantly by white fat cells. Consequently, mice with leptin deficiency are obese.²⁰⁶ PPAR γ mRNA levels are significantly increased in fatty livers of leptin deficiency mice.²⁰⁷ The activation of PPAR γ causes fatty liver. There are two PPAR γ isoforms (γ 1 and γ 2), and both forms are detectable in hepatocytes. Ethanol increases the mRNA levels of both isoforms and the expression level of downstream target fatty-acid translocase (CD36), a membrane receptor responsible for the uptake of modified forms of low-density lipoproteins and fatty acids from circulation.^{186,208} PPAR γ is also regulated by chronic alcohol exposure in Kupffer cells and hepatocytes.^{209,210} Treatment with the PPAR γ agonist pioglitazone prevents the development of alcohol-induced steatosis and inflammation.²¹¹ PGC-1 α , a co-activator of PPAR γ , is essential for the induction of many ROS-detoxifying enzymes, including GPx1 and SOD2.^{212,213} Thus, the role of PGC-1 α in ALD warrants investigation.

LXR, PXR, CAR and other lipogenic transcription factors

LXR α and LXR β might play a role in ALD due to their actions in lipid homeostasis and inflammation.^{214–217} The effect of LXR on lipogenesis involves both direct and indirect mechanisms. LXR/RXR heterodimers bind lipogenic gene promoters, such as FAS, or regulate lipogenic gene expression by controlling levels of SREBP-1c, a transcriptional factor known to regulate the expression of a battery of lipogenic enzymes.²¹⁸ The activation of SREBP-1c by ethanol feeding was associated with increased expression of lipogenic genes as well as the accumulation of triglyceride in the livers of mice.²¹⁹ Transcriptional targets of SREBP-1c include FAS, ACC, stearoyl CoA desaturase (SCD) and fatty acid elongase (FAE).^{215,217,220} SREBP-2 is important for the cholesterol biosynthesis pathway; it regulates HMG-CoA synthase, HMG-CoA reductase, farnesyl diphosphate synthase and squalene synthase.²²¹

Other NRs that are linked to steatosis are FXR, HNF4 α , CAR and PXR. The activation of FXR by bile acids reduces triglyceride levels.^{222–225} The triglyceride lowering effect of bile acids is likely mediated through FXR-induced PPAR α activation.²²⁶ FXR represses lipogenesis by interfering with the expression of SREBP-1c through SHP, which inhibits the activity of LXR.²²⁵ As expected, FXR-null mice exhibit massive steatosis when challenged with a high cholesterol/high fat diet.²²⁷ HNF4 α functions as a homodimer and is constitutively active through binding of integral fatty acids.^{228,229} HNF4 α is central to the maintenance of hepatocyte differentiation and is a major *in vivo* regulator of bile acid and

lipid homeostasis genes.²³⁰ Hepatocyte HNF4 α -deficient mice have hepatic lipid accumulation and reduced serum cholesterol and triglyceride levels.²³⁰ HNF4 α is involved in the regulation of gene transcription mediated by PXR, CAR and LXR.^{231,232}

Recent studies have also linked CAR to both lipid and glucose metabolism.^{233,234} Like PPAR α , fasting-induced increases in fatty acids and PPAR α agonists induce CAR expression.^{233,235,236} The activation of CAR suppresses lipid metabolism and reduces serum triglyceride by decreasing the active form of SREBP-1c.²³⁷ The xenobiotic receptor PXR regulates an SREBP-independent lipogenic pathway by up-regulating the expression of free fatty acid uptake transporter CD36 and several accessory lipogenic enzymes, including SCD-1 and long-chain FAE.²³⁸ PPAR γ and CD36 are direct transcriptional targets of PXR.²³⁸ The activation of PXR in mice could induce hepatic triglyceride accumulation in an SREBP-1c-independent manner.²³⁸ Hepatic PXR mRNA levels are significantly increased in mice fed MCD diet.²³⁹ Furthermore, CAR or PXR ligands can increase levels of insulin-induced gene-1, a protein with antilipogenic properties.²⁴⁰ The role of these receptors in ALD remains to be examined. Figure 2 summarizes the role of NRs in lipid homeostasis.

Conclusions

In summary, the molecular mechanisms leading to ALD are complex. Current research on the role of NRs in ALD has focused mainly on PPARs. Our recent publication shows the hepatoprotective role of PXR in lipopolysaccharide and galactosamine-induced liver injury.²⁴¹ Given the pivotal roles of LXR, HNF4 α , FXR, CAR and PXR in lipid metabolism, energy homeostasis, bile acid homeostasis and inflammation, attention should now be devoted to these NRs. It is likely that new insights into the pathogenesis of ALD could be achieved via this endeavor. Furthermore, variable NR expression levels may determine target gene expression levels and susceptibility to ALD. Reports indicate that a single-nucleotide polymorphism in the PPAR γ gene is associated with the susceptibility to non-alcoholic fatty liver disease in Chinese people.²⁴² Genetic polymorphism of NRs in contribution to ALD should be studied.

Our published data showed that hepatocyte RXR α , a partner for class II NR superfamily members, plays a significant role in lipid homeostasis, inflammatory process and even alcohol detoxification.^{44,46,123,140,142,143,158} Thus, the expression level and functional activity of hepatocyte RXR α should have a significant impact on the disease process. It is important to note that the role of NRs in ALD might be liver cell-type specific. Increased inflammatory responses found in hepatocyte RXR α -KO mice suggests the presence of cross-talk between hepatocyte RXR α and the inflammatory response generated from Kupffer cells. Thus, organ- and cell-type-specific KO mice might be necessary to define the role of each NR in ALD.

Acknowledgments

This work was supported by NIH Grants CA 53596 and AA14147. The authors thank Mr Nathan Bushue and David Johnson for editing this manuscript.

References

1. Liu JD, Leung KW, Wang CK, Liao LY, Wang CS, Chen PH, Chen CC, Yeh EK. Alcohol-related problems in Taiwan with particular emphasis on alcoholic liver diseases. *Alcohol Clin Exp Res.* 1998; 22:164S–9S. [PubMed: 9622397]
2. Pares A, Caballeria J, Bruguera M, Torres M, Rodes J. Histological course of alcoholic hepatitis. Influence of abstinence, sex and extent of hepatic damage. *J Hepatol.* 1986; 2:33–42. [PubMed: 3950362]

3. Stewart S, Jones D, Day CP. Alcoholic liver disease: new insights into mechanisms and preventative strategies. *Trends Mol Med*. 2001; 7:408–13. [PubMed: 11530336]
4. Morgan TR, Mandayam S, Jamal MM. Alcohol and hepatocellular carcinoma. *Gastroenterology*. 2004; 127:S87–96. [PubMed: 15508108]
5. Stickel F, Schuppan D, Hahn EG, Seitz HK. Cocarcinogenic effects of alcohol in hepatocarcinogenesis. *Gut*. 2002; 51:132–9. [PubMed: 12077107]
6. Becker U, Deis A, Sorensen TI, Gronbaek M, Borch-Johnsen K, Muller CF, Schnohr P, Jensen G. Prediction of risk of liver disease by alcohol intake, sex, and age: a prospective population study. *Hepatology*. 1996; 23:1025–9. [PubMed: 8621128]
7. Bouchier IA, Hislop WS, Prescott RJ. A prospective study of alcoholic liver disease and mortality. *J Hepatol*. 1992; 16:290–7. [PubMed: 1487605]
8. Klatsky AL, Armstrong MA, Friedman GD. Alcohol and mortality. *Ann Intern Med*. 1992; 117:646–54. [PubMed: 1530196]
9. Mandayam S, Jamal MM, Morgan TR. Epidemiology of alcoholic liver disease. *Semin Liver Dis*. 2004; 24:217–32. [PubMed: 15349801]
10. Teli MR, Day CP, Burt AD, Bennett MK, James OF. Determinants of progression to cirrhosis or fibrosis in pure alcoholic fatty liver. *Lancet*. 1995; 346:987–90. [PubMed: 7475591]
11. Jamal MM, Morgan TR. Liver disease in alcohol and hepatitis C. *Best Pract Res Clin Gastroenterol*. 2003; 17:649–62. [PubMed: 12828960]
12. Pageaux GP, Bismuth M, Perney P, Costes V, Jaber S, Possoz P, Fabre JM, Navarro F, Blanc P, Domergue J, Eledjam JJ, Larrey D. Alcohol relapse after liver transplantation for alcoholic liver disease: does it matter? *J Hepatol*. 2003; 38:629–34. [PubMed: 12713874]
13. Roizen R, Kerr WC, Fillmore KM. Cirrhosis mortality and per capita consumption of distilled spirits, United States, 1949–94: trend analysis. *BMJ*. 1999; 319:666–70. [PubMed: 10480821]
14. Crabb DW, Matsumoto M, Chang D, You M. Overview of the role of alcohol dehydrogenase and aldehyde dehydrogenase and their variants in the genesis of alcohol-related pathology. *Proc Nutr Soc*. 2004; 63:49–63. [PubMed: 15099407]
15. Konishi T, Calvillo M, Leng AS, Feng J, Lee T, Lee H, Smith JL, Sial SH, Berman N, French S, Eysselein V, Lin KM, Wan YJ. The ADH3*2 and CYP2E1 c2 alleles increase the risk of alcoholism in Mexican American men. *Exp Mol Pathol*. 2003; 74:183–9. [PubMed: 12710951]
16. Konishi T, Luo HR, Calvillo M, Mayo MS, Lin KM, Wan YJ. ADH1B*1, ADH1C*2, DRD2 (–141C Ins), and 5-HTTLPR are associated with alcoholism in Mexican American men living in Los Angeles. *Alcohol Clin Exp Res*. 2004; 28:1145–52. [PubMed: 15318112]
17. Wan YJ, Poland RE, Lin KM. Genetic polymorphism of CYP2E1, ADH2, and ALDH2 in Mexican-Americans. *Genet Test*. 1998; 2:79–83. [PubMed: 10464602]
18. Zakhari S, Li TK. Determinants of alcohol use and abuse: impact of quantity and frequency patterns on liver disease. *Hepatology*. 2007; 46:2032–9. [PubMed: 18046720]
19. Bellentani S, Saccoccio G, Costa G, Tiribelli C, Manenti F, Sodde M, Saveria Croce L, Sasso F, Pozzato G, Cristianini G, Brandi G. Drinking habits as cofactors of risk for alcohol induced liver damage. The Dionysos Study Group. *Gut*. 1997; 41:845–50. [PubMed: 9462221]
20. Grove J, Daly AK, Bassendine MF, Day CP. Association of a tumor necrosis factor promoter polymorphism with susceptibility to alcoholic steatohepatitis. *Hepatology*. 1997; 26:143–6. [PubMed: 9214463]
21. Hrubec Z, Omenn GS. Evidence of genetic predisposition to alcoholic cirrhosis and psychosis: twin concordances for alcoholism and its biological end points by zygosity among male veterans. *Alcohol Clin Exp Res*. 1981; 5:207–15. [PubMed: 7018299]
22. Ladero JM, Martinez C, Garcia-Martin E, Fernandez-Arquero M, Lopez-Alonso G, de la Concha EG, Diaz-Rubio M, Agundez JA. Polymorphisms of the glutathione S-transferases mu-1 (GSTM1) and theta-1 (GSTT1) and the risk of advanced alcoholic liver disease. *Scand J Gastroenterol*. 2005; 40:348–53. [PubMed: 15932176]
23. Naveau S, Giraud V, Borotto E, Aubert A, Capron F, Chaput JC. Excess weight risk factor for alcoholic liver disease. *Hepatology*. 1997; 25:108–11. [PubMed: 8985274]

24. Savolainen VT, Pjarinen J, Perola M, Penttilä A, Karhunen PJ. Glutathione-S-transferase GST M1 “null” genotype and the risk of alcoholic liver disease. *Alcohol Clin Exp Res.* 1996; 20:1340–5. [PubMed: 8947308]
25. Wiley TE, McCarthy M, Breidi L, Layden TJ. Impact of alcohol on the histological and clinical progression of hepatitis C infection. *Hepatology.* 1998; 28:805–9. [PubMed: 9731576]
26. Wilfred de Alwis NM, Day CP. Genetics of alcoholic liver disease and nonalcoholic fatty liver disease. *Semin Liver Dis.* 2007; 27:44–54. [PubMed: 17295176]
27. Stinson FS, Grant BF, Dufour MC. The critical dimension of ethnicity in liver cirrhosis mortality statistics. *Alcohol Clin Exp Res.* 2001; 25:1181–7. [PubMed: 11505049]
28. Gunzerath L, Goldman D. G × E: a NIAAA workshop on gene–environment interactions. *Alcohol Clin Exp Res.* 2003; 27:540–62. [PubMed: 12658122]
29. Eriksson CJ, Fukunaga T, Sarkola T, Chen WJ, Chen CC, Ju JM, Cheng AT, Yamamoto H, Kohlenberg-Muller K, Kimura M, Murayama M, Matsushita S, Kashima H, Higuchi S, Carr L, Viljoen D, Brooke L, Stewart T, Foroud T, Su J, Li TK, Whitfield JB. Functional relevance of human adh polymorphism. *Alcohol Clin Exp Res.* 2001; 25:157S–63S. [PubMed: 11391066]
30. Li TK, Yin SJ, Crabb DW, O’Connor S, Ramchandani VA. Genetic and environmental influences on alcohol metabolism in humans. *Alcohol Clin Exp Res.* 2001; 25:136–44. [PubMed: 11198709]
31. Mulligan CJ, Robin RW, Osier MV, Sambughin N, Goldfarb LG, Kittles RA, Hesselbrock D, Goldman D, Long JC. Allelic variation at alcohol metabolism genes (ADH1B, ADH1C, ALDH2) and alcohol dependence in an American Indian population. *Hum Genet.* 2003; 113:325–36. [PubMed: 12884000]
32. Sass DA, Shaikh OS. Alcoholic hepatitis. *Clin Liver Dis.* 2006; 10:219–37. vii. [PubMed: 16971259]
33. Niemela O, Parkkila S, Yla-Herttuala S, Villanueva J, Ruebner B, Halsted CH. Sequential acetaldehyde production, lipid peroxidation, and fibrogenesis in micropig model of alcohol-induced liver disease. *Hepatology.* 1995; 22:1208–14. [PubMed: 7557872]
34. Sladek NE, Manthey CL, Maki PA, Zhang Z, Landkamer GJ. Xenobiotic oxidation catalyzed by aldehyde dehydrogenases. *Drug Metab Rev.* 1989; 20:697–720. [PubMed: 2680404]
35. Crabb DW. Recent developments in alcoholism: the liver. *Recent Dev Alcohol.* 1993; 11:207–30. [PubMed: 8234924]
36. Fromenty B, Berson A, Pessayre D. Microvesicular steatosis and steatohepatitis: role of mitochondrial dysfunction and lipid peroxidation. *J Hepatol.* 1997; 26(Suppl 1):13–22. [PubMed: 9138124]
37. Grunnet N, Kondrup J. The effect of ethanol on the β -oxidation of fatty acids. *Alcohol Clin Exp Res.* 1986; 10:64S–8S. [PubMed: 3544932]
38. Lieber CS. Alcoholic fatty liver: its pathogenesis and mechanism of progression to inflammation and fibrosis. *Alcohol.* 2004; 34:9–19. [PubMed: 15670660]
39. Day CP, James OF. Hepatic steatosis: innocent bystander or guilty party? *Hepatology.* 1998; 27:1463–6. [PubMed: 9620314]
40. Liu C, Russell RM, Seitz HK, Wang XD. Ethanol enhances retinoic acid metabolism into polar metabolites in rat liver via induction of cytochrome P4502E1. *Gastroenterology.* 2001; 120:179–89. [PubMed: 11208727]
41. Wang XD. Alcohol, vitamin A, and cancer. *Alcohol.* 2005; 35:251–8. [PubMed: 16054987]
42. Gouillon Z, Lucas D, Li J, Hagbjork AL, French BA, Fu P, Fang C, Ingelman-Sundberg M, Donohue TM Jr, French SW. Inhibition of ethanol-induced liver disease in the intragastric feeding rat model by chlormethiazole. *Proc Soc Exp Biol Med.* 2000; 224:302–8. [PubMed: 10964266]
43. Barak AJ, Beckenhauer HC, Tuma DJ. Methionine synthase. A possible prime site of the ethanolic lesion in liver. *Alcohol.* 2002; 26:65–7. [PubMed: 12007580]
44. Dai T, Wu Y, Leng AS, Ao Y, Robel RC, Lu SC, French SW, Wan YJ. RXR α -regulated liver SAME and GSH levels influence susceptibility to alcohol-induced hepatotoxicity. *Exp Mol Pathol.* 2003; 75:194–200. [PubMed: 14611810]
45. Gyamfi MA, Damjanov I, French S, Wan YJ. The pathogenesis of ethanol versus methionine and choline deficient diet-induced liver injury. *Biochem Pharmacol.* 2008; 75:981–95. [PubMed: 18036573]

46. Gyamfi MA, He L, French SW, Damjanov I, Wan YJ. Hepatocyte retinoid X receptor α -dependent regulation of lipid homeostasis and inflammatory cytokine expression contributes to alcohol-induced liver injury. *J Pharmacol Exp Ther*. 2008; 324:443–53. [PubMed: 17975011]
47. Ji C, Chan C, Kaplowitz N. Predominant role of sterol response element binding proteins (SREBP) lipogenic pathways in hepatic steatosis in the murine intragastric ethanol feeding model. *J Hepatol*. 2006; 45:1717–24. [PubMed: 16879892]
48. Ji C, Shinohara M, Kuhlenskamp J, Chan C, Kaplowitz N. Mechanisms of protection by the β ne-homocysteine methyltransferase/ β ne system in HepG2 cells and primary mouse hepatocytes. *Hepatology*. 2007; 46:1586–96. [PubMed: 17705221]
49. Lee TD, Sadda MR, Mendler MH, Bottiglieri T, Kanel G, Mato JM, Lu SC. Abnormal hepatic methionine and glutathione metabolism in patients with alcoholic hepatitis. *Alcohol Clin Exp Res*. 2004; 28:173–81. [PubMed: 14745316]
50. Lu SC, Tsukamoto H, Mato JM. Role of abnormal methionine metabolism in alcoholic liver injury. *Alcohol*. 2002; 27:155–62. [PubMed: 12163143]
51. Barak AJ, Beckenhauer HC, Tuma DJ, Badakhsh S. Effects of prolonged ethanol feeding on methionine metabolism in rat liver. *Biochem Cell Biol*. 1987; 65:230–3. [PubMed: 3580171]
52. Barak AJ, Beckenhauer HC, Tuma DJ. β ne effects on hepatic methionine metabolism elicited by short-term ethanol feeding. *Alcohol*. 1996; 13:483–6. [PubMed: 8888945]
53. Ji C, Kaplowitz N. β ne decreases hyperhomocysteinemia, endoplasmic reticulum stress, and liver injury in alcohol-fed mice. *Gastroenterology*. 2003; 124:1488–99. [PubMed: 12730887]
54. Kaplowitz N, Than TA, Shinohara M, Ji C. Endoplasmic reticulum stress and liver injury. *Semin Liver Dis*. 2007; 27:367–77. [PubMed: 17979073]
55. Apte UM, Banerjee A, McRee R, Wellberg E, Ramaiah SK. Role of osteopontin in hepatic neutrophil infiltration during alcoholic steatohepatitis. *Toxicol Appl Pharmacol*. 2005; 207:25–38. [PubMed: 15885730]
56. Banerjee A, Burghardt RC, Johnson GA, White FJ, Ramaiah SK. The temporal expression of osteopontin (SPP-1) in the rodent model of alcoholic steatohepatitis: a potential biomarker. *Toxicol Pathol*. 2006; 34:373–84. [PubMed: 16844665]
57. Alessi MC, Bastelica D, Mavri A, Morange P, Berthet B, Grino M, Juhan-Vague I. Plasma PAI-1 levels are more strongly related to liver steatosis than to adipose tissue accumulation. *Arterioscler Thromb Vasc Biol*. 2003; 23:1262–8. [PubMed: 12750120]
58. Arteel GE. New role of plasminogen activator inhibitor-1 in alcohol-induced liver injury. *J Gastroenterol Hepatol*. 2008; 23(Suppl 1):S54–9. [PubMed: 18336665]
59. Berghheim I, Guo L, Davis MA, Lambert JC, Beier JI, Duveau I, Luyendyk JP, Roth RA, Arteel GE. Metformin prevents alcohol-induced liver injury in the mouse: critical role of plasminogen activator inhibitor-1. *Gastroenterology*. 2006; 130:2099–112. [PubMed: 16762632]
60. Ma J, Weisberg A, Griffin JP, Vaughan DE, Fogo AB, Brown NJ. Plasminogen activator inhibitor-1 deficiency protects against aldosterone-induced glomerular injury. *Kidney Int*. 2006; 69:1064–72. [PubMed: 16528256]
61. Wolak T, Kim H, Ren Y, Kim J, Vaziri ND, Nicholas SB. Osteopontin modulates angiotensin II-induced inflammation, oxidative stress, and fibrosis of the kidney. *Kidney Int*. 2009; 76:32–43. [PubMed: 19357716]
62. Qin X, Gao B. The complement system in liver diseases. *Cell Mol Immunol*. 2006; 3:333–40. [PubMed: 17092430]
63. Bykov I, Jauhiainen M, Olkkonen VM, Saarikoski ST, Ehnholm C, Junnikkala S, Vakeva A, Lindros KO, Meri S. Hepatic gene expression and lipid parameters in complement C3(–/–) mice that do not develop ethanol-induced steatosis. *J Hepatol*. 2007; 46:907–14. [PubMed: 17321001]
64. Bykov I, Junnikkala S, Pekna M, Lindros KO, Meri S. Effect of chronic ethanol consumption on the expression of complement components and acute-phase proteins in liver. *Clin Immunol*. 2007; 124:213–20. [PubMed: 17586095]
65. Bykov IL, Vakeva A, Jarvelainen HA, Meri S, Lindros KO. Protective function of complement against alcohol-induced rat liver damage. *Int Immunopharmacol*. 2004; 4:1445–54. [PubMed: 15351314]

66. Jarvelainen HA, Vakeva A, Lindros KO, Meri S. Activation of complement components and reduced regulator expression in alcohol-induced liver injury in the rat. *Clin Immunol.* 2002; 105:57–63. [PubMed: 12483994]
67. Pritchard MT, McMullen MR, Stavitsky AB, Cohen JI, Lin F, Medof ME, Nagy LE. Differential contributions of C3, C5, and decay-accelerating factor to ethanol-induced fatty liver in mice. *Gastroenterology.* 2007; 132:1117–26. [PubMed: 17383432]
68. Hong F, Kim WH, Tian Z, Jaruga B, Ishac E, Shen X, Gao B. Elevated interleukin-6 during ethanol consumption acts as a potential endogenous protective cytokine against ethanol-induced apoptosis in the liver: involvement of induction of Bcl-2 and Bcl-x(L) proteins. *Oncogene.* 2002; 21:32–43. [PubMed: 11791174]
69. Hong F, Radaeva S, Pan HN, Tian Z, Veech R, Gao B. Interleukin 6 alleviates hepatic steatosis and ischemia/reperfusion injury in mice with fatty liver disease. *Hepatology.* 2004; 40:933–41. [PubMed: 15382116]
70. Gong P, Cederbaum AI. Nrf2 is increased by CYP2E1 in rodent liver and HepG2 cells and protects against oxidative stress caused by CYP2E1. *Hepatology.* 2006; 43:144–53. [PubMed: 16374848]
71. Lamle J, Marhenke S, Borlak J, von Wasielewski R, Eriksson CJ, Geffers R, Manns MP, Yamamoto M, Vogel A. Nuclear factor- κ B-related factor 2 prevents alcohol-induced fulminant liver injury. *Gastroenterology.* 2008; 134:1159–68. [PubMed: 18395094]
72. Berg AH, Combs TP, Scherer PE. ACRP30/adiponectin: an adipokine regulating glucose and lipid metabolism. *Trends Endocrinol Metab.* 2002; 13:84–9. [PubMed: 11854024]
73. Maeda N, Shimomura I, Kishida K, Nishizawa H, Matsuda M, Nagaretani H, Furuyama N, Kondo H, Takahashi M, Arita Y, Komuro R, Ouchi N, Kihara S, Tochino Y, Okutomi K, Horie M, Takeda S, Aoyama T, Funahashi T, Matsuzawa Y. Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. *Nat Med.* 2002; 8:731–7. [PubMed: 12068289]
74. Shapiro L, Scherer PE. The crystal structure of a complement-1q family protein suggests an evolutionary link to tumor necrosis factor. *Curr Biol.* 1998; 8:335–8. [PubMed: 9512423]
75. Xu A, Wang Y, Keshaw H, Xu LY, Lam KS, Cooper GJ. The fat-derived hormone adiponectin alleviates alcoholic and nonalcoholic fatty liver diseases in mice. *J Clin Invest.* 2003; 112:91–100. [PubMed: 12840063]
76. Yokota T, Oritani K, Takahashi I, Ishikawa J, Matsuyama A, Ouchi N, Kihara S, Funahashi T, Tenner AJ, Tomiyama Y, Matsuzawa Y. Adiponectin, a new member of the family of soluble defense collagens, negatively regulates the growth of myelomonocytic progenitors and the functions of macrophages. *Blood.* 2000; 96:1723–32. [PubMed: 10961870]
77. Esfandiari F, You M, Villanueva JA, Wong DH, French SW, Halsted CH. S-adenosylmethionine attenuates hepatic lipid synthesis in micropigs fed ethanol with a folate-deficient diet. *Alcohol Clin Exp Res.* 2007; 31:1231–9. [PubMed: 17577393]
78. Rogers CQ, Ajmo JM, You M. Adiponectin and alcoholic fatty liver disease. *IUBMB Life.* 2008; 60:790–7. [PubMed: 18709650]
79. Yamauchi T, Kamon J, Minokoshi Y, Ito Y, Waki H, Uchida S, Yamashita S, Noda M, Kita S, Ueki K, Eto K, Akanuma Y, Froguel P, Foufelle F, Ferre P, Carling D, Kimura S, Nagai R, Kahn BB, Kadowaki T. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. *Nat Med.* 2002; 8:1288–95. [PubMed: 12368907]
80. Yamauchi T, Kamon J, Waki H, Imai Y, Shimozawa N, Hioki K, Uchida S, Ito Y, Takakuwa K, Matsui J, Takata M, Eto K, Terauchi Y, Komeda K, Tsunoda M, Murakami K, Ohnishi Y, Naitoh T, Yamamura K, Ueyama Y, Froguel P, Kimura S, Nagai R, Kadowaki T. Globular adiponectin protected ob/ob mice from diabetes and ApoE-deficient mice from atherosclerosis. *J Biol Chem.* 2003; 278:2461–8. [PubMed: 12431986]
81. Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, Mori Y, Ide T, Murakami K, Tsuboyama-Kasaoka N, Ezaki O, Akanuma Y, Gavrilova O, Vinson C, Reitman ML, Kagechika H, Shudo K, Yoda M, Nakano Y, Tobe K, Nagai R, Kimura S, Tomita M, Froguel P, Kadowaki T. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipodystrophy and obesity. *Nat Med.* 2001; 7:941–6. [PubMed: 11479627]

82. You M, Considine RV, Leone TC, Kelly DP, Crabb DW. Role of adiponectin in the protective action of dietary saturated fat against alcoholic fatty liver in mice. *Hepatology*. 2005; 42:568–77. [PubMed: 16108051]
83. Long YC, Zierath JR. AMP-activated protein kinase signaling in metabolic regulation. *J Clin Invest*. 2006; 116:1776–83. [PubMed: 16823475]
84. Hardie DG, Carling D, Carlson M. The AMP-activated/SNF1 protein kinase subfamily: metabolic sensors of the eukaryotic cell? *Annu Rev Biochem*. 1998; 67:821–55. [PubMed: 9759505]
85. Winder WW, Hardie DG. AMP-activated protein kinase, a metabolic master switch: possible roles in type 2 diabetes. *Am J Physiol*. 1999; 277:E1–10. [PubMed: 10409121]
86. Giandomenico V, Simonsson M, Gronroos E, Ericsson J. Coactivator-dependent acetylation stabilizes members of the SREBP family of transcription factors. *Mol Cell Biol*. 2003; 23:2587–99. [PubMed: 12640139]
87. You M, Liang X, Ajmo JM, Ness GC. Involvement of mammalian sirtuin 1 in the action of ethanol in the liver. *Am J Physiol Gastrointest Liver Physiol*. 2008; 294:G892–8. [PubMed: 18239056]
88. Ajmo JM, Liang X, Rogers CQ, Pennock B, You M. Resveratrol alleviates alcoholic fatty liver in mice. *Am J Physiol Gastrointest Liver Physiol*. 2008; 295:G833–42. [PubMed: 18755807]
89. Rodgers JT, Puigserver P. Fasting-dependent glucose and lipid metabolic response through hepatic sirtuin 1. *Proc Natl Acad Sci USA*. 2007; 104:12861–6. [PubMed: 17646659]
90. Lin HZ, Yang SQ, Zeldin G, Diehl AM. Chronic ethanol consumption induces the production of tumor necrosis factor- α and related cytokines in liver and adipose tissue. *Alcohol Clin Exp Res*. 1998; 22:231, S7S. [PubMed: 9514312]
91. French SW. Intragastric ethanol infusion model for cellular and molecular studies of alcoholic liver disease. *J Biomed Sci*. 2001; 8:20–7. [PubMed: 11173972]
92. Lieber CS, DeCarli LM. Liquid diet technique of ethanol administration: 1989 update. *Alcohol Alcohol*. 1989; 24:197–211. [PubMed: 2667528]
93. Lieber CS, DeCarli LM, Sorrell MF. Experimental methods of ethanol administration. *Hepatology*. 1989; 10:501–10. [PubMed: 2673971]
94. Tsukamoto H, Horne W, Kamimura S, Niemela O, Parkkila S, Yla-Herttuala S, Brittenham GM. Experimental liver cirrhosis induced by alcohol and iron. *J Clin Invest*. 1995; 96:620–30. [PubMed: 7615836]
95. Tsukamoto H, French SW, Benson N, Delgado G, Rao GA, Larkin EC, Largman C. Severe and progressive steatosis and focal necrosis in rat liver induced by continuous intragastric infusion of ethanol and low fat diet. *Hepatology*. 1985; 5:224–32. [PubMed: 3979954]
96. Tsukamoto H, Reidelberger RD, French SW, Largman C. Long-term cannulation model for blood sampling and intragastric infusion in the rat. *Am J Physiol*. 1984; 247:R595–9. [PubMed: 6433728]
97. Kono H, Rusyn I, Uesugi T, Yamashina S, Connor HD, Dikalova A, Mason RP, Thurman RG. Diphenyleneiodonium sulfate, an NADPH oxidase inhibitor, prevents early alcohol-induced liver injury in the rat. *Am J Physiol Gastrointest Liver Physiol*. 2001; 280:G1005–12. [PubMed: 11292610]
98. Lieber CS, DeCarli LM. Quantitative relationship between amount of dietary fat and severity of alcoholic fatty liver. *Am J Clin Nutr*. 1970; 23:474–8. [PubMed: 5462407]
99. Lieber CS, Spritz N. Effects of prolonged ethanol intake in man: role of dietary adipose, and endogenously synthesized fatty acids in the pathogenesis of the alcoholic fatty liver. *J Clin Invest*. 1966; 45:1400–11. [PubMed: 4162127]
100. Mezey E. Dietary fat and alcoholic liver disease. *Hepatology*. 1998; 28:901–5. [PubMed: 9755223]
101. Bloom RJ, Westerfeld WW. The thiobarbituric acid reaction in relation to fatty livers. *Arch Biochem Biophys*. 1971; 145:669–75. [PubMed: 5125212]
102. Nanji AA. Role of different dietary fatty acids in the pathogenesis of experimental alcoholic liver disease. *Alcohol*. 2004; 34:21–5. [PubMed: 15670661]
103. Nanji AA, Mendenhall CL, French SW. Beef fat prevents alcoholic liver disease in the rat. *Alcohol Clin Exp Res*. 1989; 13:15–19. [PubMed: 2646971]

104. Nanji AA, Sadrzadeh SM, Yang EK, Fogt F, Meydani M, Dannenberg AJ. Dietary saturated fatty acids: a novel treatment for alcoholic liver disease. *Gastroenterology*. 1995; 109:547–54. [PubMed: 7615205]
105. Ronis MJ, Korourian S, Zipperman M, Hakkak R, Badger TM. Dietary saturated fat reduces alcoholic hepatotoxicity in rats by altering fatty acid metabolism and membrane composition. *J Nutr*. 2004; 134:904–12. [PubMed: 15051845]
106. Nanji AA, Jokelainen K, Tipoe GL, Rahemtulla A, Dannenberg AJ. Dietary saturated fatty acids reverse inflammatory and fibrotic changes in rat liver despite continued ethanol administration. *J Pharmacol Exp Ther*. 2001; 299:638–44. [PubMed: 11602676]
107. Nanji AA, Yang EK, Fogt F, Sadrzadeh SM, Dannenberg AJ. Medium chain triglycerides and vitamin E reduce the severity of established experimental alcoholic liver disease. *J Pharmacol Exp Ther*. 1996; 277:1694–700. [PubMed: 8667240]
108. Carson EJ, Pruett SB. Development and characterization of a binge drinking model in mice for evaluation of the immunological effects of ethanol. *Alcohol Clin Exp Res*. 1996; 20:132–8. [PubMed: 8651442]
109. Kim SJ, Lee JW, Jung YS, Kwon do Y, Park HK, Ryu CS, Kim SK, Oh GT, Kim YC. Ethanol-induced liver injury and changes in sulfur amino acid metabolomics in glutathione peroxidase and catalase double knockout mice. *J Hepatol*. 2009; 50:1184–91. [PubMed: 19398231]
110. McCuskey RS, Bethea NW, Wong J, McCuskey MK, Abril ER, Wang X, Ito Y, DeLeve LD. Ethanol bingeing exacerbates sinusoidal endothelial and parenchymal injury elicited by acetaminophen. *J Hepatol*. 2005; 42:371–7. [PubMed: 15710220]
111. Pruett SB, Zheng Q, Fan R, Matthews K, Schwab C. Ethanol suppresses cytokine responses induced through Toll-like receptors as well as innate resistance to *Escherichia coli* in a mouse model for binge drinking. *Alcohol*. 2004; 33:147–55. [PubMed: 15528012]
112. McCarty CA, Ebel BE, Garrison MM, DiGiuseppe DL, Christakis DA, Rivara FP. Continuity of binge and harmful drinking from late adolescence to early adulthood. *Pediatrics*. 2004; 114:714–9. [PubMed: 15342844]
113. Miller JW, Naimi TS, Brewer RD, Jones SE. Binge drinking and associated health risk behaviors among high school students. *Pediatrics*. 2007; 119:76–85. [PubMed: 17200273]
114. Mathurin P, Deltenre P. Effect of binge drinking on the liver: an alarming public health issue? *Gut*. 2009; 58:613–7. [PubMed: 19174416]
115. Parrish KM, Dufour MC, Stinson FS, Harford TC. Average daily alcohol consumption during adult life among decedents with and without cirrhosis: the 1986 National Mortality Followback Survey. *J Stud Alcohol*. 1993; 54:450–6. [PubMed: 8341047]
116. Sorensen TI, Orholm M, Bentsen KD, Hoybye G, Eghoje K, Christoffersen P. Prospective evaluation of alcohol abuse and alcoholic liver injury in men as predictors of development of cirrhosis. *Lancet*. 1984; 2:241–4. [PubMed: 6146805]
117. Hoffman PL, Yagi T, Tabakoff B, Phillips TJ, Kono H, Messing RO, Choi DS. Transgenic and gene “knockout” models in alcohol research. *Alcohol Clin Exp Res*. 2001; 25:60S–6S. [PubMed: 11391051]
118. Ji C, Shinohara M, Vance D, Than TA, Ookhtens M, Chan C, Kaplowitz N. Effect of transgenic extrahepatic expression of β -homocysteine methyltransferase on alcohol or homocysteine-induced fatty liver. *Alcohol Clin Exp Res*. 2008; 32:1049–58. [PubMed: 18498552]
119. Lee JH, Banerjee A, Ueno Y, Ramaiah SK. Potential relationship between hepatobiliary osteopontin and peroxisome proliferator-activated receptor α expression following ethanol-associated hepatic injury *in vivo* and *in vitro*. *Toxicol Sci*. 2008; 106:290–9. [PubMed: 18703563]
120. Nakajima T, Kamijo Y, Tanaka N, Sugiyama E, Tanaka E, Kiyosawa K, Fukushima Y, Peters JM, Gonzalez FJ, Aoyama T. Peroxisome proliferator-activated receptor α protects against alcohol-induced liver damage. *Hepatology*. 2004; 40:972–80. [PubMed: 15382117]
121. Nanji AA, French SW. Animal models of alcoholic liver disease – focus on the intragastric feeding model. *Alcohol Res Health*. 2003; 27:325–30. [PubMed: 15540804]

122. Blanco PG, Salem RO, Ollero M, Zaman MM, Cluette-Brown JE, Freedman SD, Laposata M. Ethanol administration to cystic fibrosis knockout mice results in increased fatty acid ethyl ester production. *Alcohol Clin Exp Res*. 2005; 29:2039–45. [PubMed: 16340462]
123. Gyamfi MA, Kocsis MG, He L, Dai G, Mendy AJ, Wan YJ. The role of retinoid X receptor α in regulating alcohol metabolism. *J Pharmacol Exp Ther*. 2006; 319:360–8. [PubMed: 16829625]
124. Siegmund SV, Haas S, Singer MV. Animal models and their results in gastrointestinal alcohol research. *Dig Dis*. 2005; 23:181–94. [PubMed: 16508282]
125. Chawla A, Repa JJ, Evans RM, Mangelsdorf DJ. Nuclear receptors and lipid physiology: opening the X-files. *Science*. 2001; 294:1866–70. [PubMed: 11729302]
126. Wang H, LeCluyse EL. Role of orphan nuclear receptors in the regulation of drug-metabolising enzymes. *Clin Pharmacokinet*. 2003; 42:1331–57. [PubMed: 14674787]
127. Yang X, Downes M, Yu RT, Bookout AL, He W, Straume M, Mangelsdorf DJ, Evans RM. Nuclear receptor expression links the circadian clock to metabolism. *Cell*. 2006; 126:801–10. [PubMed: 16923398]
128. Mangelsdorf DJ, Evans RM. The RXR heterodimers and orphan receptors. *Cell*. 1995; 83:841–50. [PubMed: 8521508]
129. Giguere V. Orphan nuclear receptors: from gene to function. *Endocr Rev*. 1999; 20:689–725. [PubMed: 10529899]
130. Masuda N, Yasumo H, Tamura T, Hashiguchi N, Furusawa T, Tsukamoto T, Sadano H, Osumi T. An orphan nuclear receptor lacking a zinc-finger DNA-binding domain: interaction with several nuclear receptors. *Biochim Biophys Acta*. 1997; 1350:27–32. [PubMed: 9003453]
131. Seol W, Choi HS, Moore DD. An orphan nuclear hormone receptor that lacks a DNA binding domain and heterodimerizes with other receptors. *Science*. 1996; 272:1336–9. [PubMed: 8650544]
132. Shulman AI, Larson C, Mangelsdorf DJ, Ranganathan R. Structural determinants of allosteric ligand activation in RXR heterodimers. *Cell*. 2004; 116:417–29. [PubMed: 15016376]
133. Heyman RA, Mangelsdorf DJ, Dyck JA, Stein RB, Eichele G, Evans RM, Thaller C. 9-*Cis* retinoic acid is a high affinity ligand for the retinoid X receptor. *Cell*. 1992; 68:397–406. [PubMed: 1310260]
134. Mangelsdorf DJ, Borgmeyer U, Heyman RA, Zhou JY, Ong ES, Oro AE, Kakizuka A, Evans RM. Characterization of three RXR genes that mediate the action of 9-*cis* retinoic acid. *Genes Dev*. 1992; 6:329–44. [PubMed: 1312497]
135. Kastner P, Mark M, Leid M, Gansmuller A, Chin W, Grondona JM, Decimo D, Krezel W, Dierich A, Chambon P. Abnormal spermatogenesis in RXR β mutant mice. *Genes Dev*. 1996; 10:80–92. [PubMed: 8557197]
136. Krezel W, Dupe V, Mark M, Dierich A, Kastner P, Chambon P. RXR γ null mice are apparently normal and compound RXR α +/– /RXR β – / – /RXR γ – / – mutant mice are viable. *Proc Natl Acad Sci USA*. 1996; 93:9010–4. [PubMed: 8799145]
137. Kastner P, Grondona JM, Mark M, Gansmuller A, LeMeur M, Decimo D, Vonesch JL, Dolle P, Chambon P. Genetic analysis of RXR α developmental function: convergence of RXR and RAR signaling pathways in heart and eye morphogenesis. *Cell*. 1994; 78:987–1003. [PubMed: 7923367]
138. Sucov HM, Dyson E, Gumeringer CL, Price J, Chien KR, Evans RM. RXR α mutant mice establish a genetic basis for vitamin A signaling in heart morphogenesis. *Genes Dev*. 1994; 8:1007–18. [PubMed: 7926783]
139. Leid M, Kastner P, Lyons R, Nakshatri H, Saunders M, Zacharewski T, Chen JY, Staub A, Garnier JM, Mader S, Chambon P. Purification, cloning, and RXR identity of the HeLa cell factor with which RAR or TR heterodimerizes to bind target sequences efficiently. *Cell*. 1992; 68:377–95. [PubMed: 1310259]
140. Wan YJ, An D, Cai Y, Repa JJ, Hung-Po Chen T, Flores M, Postic C, Magnuson MA, Chen J, Chien KR, French S, Mangelsdorf DJ, Sucov HM. Hepatocyte-specific mutation establishes retinoid X receptor α as a heterodimeric integrator of multiple physiological processes in the liver. *Mol Cell Biol*. 2000; 20:4436–44. [PubMed: 10825207]

141. Cai Y, Konishi T, Han G, Campwala KH, French SW, Wan YJ. The role of hepatocyte RXR α in xenobiotic-sensing nuclear receptor-mediated pathways. *Eur J Pharm Sci.* 2002; 15:89–96. [PubMed: 11803135]
142. Wan YJ, Cai Y, Lungo W, Fu P, Locker J, French S, Sucov HM. Peroxisome proliferator-activated receptor α -mediated pathways are altered in hepatocyte-specific retinoid X receptor α -deficient mice. *J Biol Chem.* 2000; 275:28285–90. [PubMed: 10866995]
143. Wan YJ, Han G, Cai Y, Dai T, Konishi T, Leng AS. Hepatocyte retinoid X receptor- α -deficient mice have reduced food intake, increased body weight, and improved glucose tolerance. *Endocrinology.* 2003; 144:605–11. [PubMed: 12538623]
144. Allali-Hassani A, Peralba JM, Martras S, Farres J, Pares X. Retinoids, omega-hydroxyfatty acids and cytotoxic aldehydes as physiological substrates, and H2-receptor antagonists as pharmacological inhibitors, of human class IV alcohol dehydrogenase. *FEBS Lett.* 1998; 426:362–6. [PubMed: 9600267]
145. Duester G, Mic FA, Molotkov A. Cytosolic retinoid dehydrogenases govern ubiquitous metabolism of retinol to retinaldehyde followed by tissue-specific metabolism to retinoic acid. *Chem Biol Interact.* 2003; 143–144:201–10.
146. Yang ZN, Davis GJ, Hurley TD, Stone CL, Li TK, Bosron WF. Catalytic efficiency of human alcohol dehydrogenases for retinol oxidation and retinal reduction. *Alcohol Clin Exp Res.* 1994; 18:587–91. [PubMed: 7943659]
147. Duester G. Involvement of alcohol dehydrogenase, short-chain dehydrogenase/reductase, aldehyde dehydrogenase, and cytochrome P450 in the control of retinoid signaling by activation of retinoic acid synthesis. *Biochemistry.* 1996; 35:12221–7. [PubMed: 8823154]
148. Deltour L, Ang HL, Duester G. Ethanol inhibition of retinoic acid synthesis as a potential mechanism for fetal alcohol syndrome. *FASEB J.* 1996; 10:1050–7. [PubMed: 8801166]
149. Kim CI, Leo MA, Lieber CS. Retinol forms retinoic acid via retinal. *Arch Biochem Biophys.* 1992; 294:388–93. [PubMed: 1567193]
150. Fischer M, You M, Matsumoto M, Crabb DW. Peroxisome proliferator-activated receptor α (PPAR α) agonist treatment reverses PPAR α dysfunction and abnormalities in hepatic lipid metabolism in ethanol-fed mice. *J Biol Chem.* 2003; 278:27997–8004. [PubMed: 12791698]
151. Motomura K, Ohata M, Satre M, Tsukamoto H. Destabilization of TNF- α mRNA by retinoic acid in hepatic macrophages: implications for alcoholic liver disease. *Am J Physiol Endocrinol Metab.* 2001; 281:E420–9. [PubMed: 11500296]
152. Leo MA, Lieber CS. Hepatic vitamin A depletion in alcoholic liver injury. *N Engl J Med.* 1982; 307:597–601. [PubMed: 7202119]
153. Han CL, Liao CS, Wu CW, Hwong CL, Lee AR, Yin SJ. Contribution to first-pass metabolism of ethanol and inhibition by ethanol for retinol oxidation in human alcohol dehydrogenase family – implications for etiology of fetal alcohol syndrome and alcohol-related diseases. *Eur J Biochem.* 1998; 254:25–31. [PubMed: 9652389]
154. Klyosov AA, Rashkovetsky LG, Tahir MK, Keung WM. Possible role of liver cytosolic and mitochondrial aldehyde dehydrogenases in acetaldehyde metabolism. *Biochemistry.* 1996; 35:4445–56. [PubMed: 8605194]
155. Gyamfi MA, Wan YJ. The effect of ethanol, ethanol metabolizing enzyme inhibitors, and Vitamin E on regulating glutathione, glutathione *S*-transferase, and *S*-adenosylmethionine in mouse primary hepatocyte. *Hepatol Res.* 2006; 35:53–61. [PubMed: 16540368]
156. Wu Y, Zhang X, Bardag-Gorce F, Robel RC, Aguilo J, Chen L, Zeng Y, Hwang K, French SW, Lu SC, Wan YJ. Retinoid X receptor α regulates glutathione homeostasis and xenobiotic detoxification processes in mouse liver. *Mol Pharmacol.* 2004; 65:550–7. [PubMed: 14978233]
157. Gyamfi MA, Tanaka Y, He L, Klaassen CD, Wan YJ. Hepatic effects of a methionine-choline-deficient diet in hepatocyte RXR α -null mice. *Toxicol Appl Pharmacol.* 2009; 234:166–78. [PubMed: 18952117]
158. Wang K, Wan YJ. Nuclear receptors and inflammatory diseases. *Exp Biol Med (Maywood).* 2008; 233:496–506. [PubMed: 18375823]

159. Kim MS, Sweeney TR, Shigenaga JK, Chui LG, Moser A, Grunfeld C, Feingold KR. Tumor necrosis factor and interleukin 1 decrease RXR α , PPAR α , PPAR γ , LXR α , and the coactivators SRC-1, PGC-1 α , and PGC-1 β in liver cells. *Metabolism*. 2007; 56:267–79. [PubMed: 17224343]
160. Beigneux AP, Moser AH, Shigenaga JK, Grunfeld C, Feingold KR. The acute phase response is associated with retinoid X receptor repression in rodent liver. *J Biol Chem*. 2000; 275:16390–9. [PubMed: 10747970]
161. Ghose R, Zimmerman TL, Thevananther S, Karpen SJ. Endotoxin leads to rapid subcellular re-localization of hepatic RXR α : a novel mechanism for reduced hepatic gene expression in inflammation. *Nucl Recept*. 2004; 2:4. [PubMed: 15312234]
162. Zimmerman TL, Thevananther S, Ghose R, Burns AR, Karpen SJ. Nuclear export of retinoid X receptor α in response to interleukin-1 β -mediated cell signaling: roles for JNK and SER260. *J Biol Chem*. 2006; 281:15434–40. [PubMed: 16551633]
163. Gu X, Ke S, Liu D, Sheng T, Thomas PE, Rabson AB, Gallo MA, Xie W, Tian Y. Role of NF-kappaB in regulation of PXR-mediated gene expression: a mechanism for the suppression of cytochrome P-450 3A4 by proinflammatory agents. *J Biol Chem*. 2006; 281:17882–9. [PubMed: 16608838]
164. Baeuerle PA, Baltimore D. NF-kappa B: ten years after. *Cell*. 1996; 87:13–20. [PubMed: 8858144]
165. Barnes PJ, Karin M. Nuclear factor-kappaB: a pivotal transcription factor in chronic inflammatory diseases. *N Engl J Med*. 1997; 336:1066–71. [PubMed: 9091804]
166. Nanji AA, Jokelainen K, Rahemtulla A, Miao L, Fogt F, Matsumoto H, Tahan SR, Su GL. Activation of nuclear factor kappa B and cytokine imbalance in experimental alcoholic liver disease in the rat. *Hepatology*. 1999; 30:934–43. [PubMed: 10498645]
167. Tilg H, Diehl AM. Cytokines in alcoholic and nonalcoholic steatohepatitis. *N Engl J Med*. 2000; 343:1467–76. [PubMed: 11078773]
168. Cressman DE, Greenbaum LE, DeAngelis RA, Ciliberto G, Furth EE, Poli V, Taub R. Liver failure and defective hepatocyte regeneration in interleukin-6-deficient mice. *Science*. 1996; 274:1379–83. [PubMed: 8910279]
169. Hong F, Jaruga B, Kim WH, Radaeva S, El-Assal ON, Tian Z, Nguyen VA, Gao B. Opposing roles of STAT1 and STAT3 in T cell-mediated hepatitis: regulation by SOCS. *J Clin Invest*. 2002; 110:1503–13. [PubMed: 12438448]
170. Gonzalez-Quintela A, Vidal C, Lojo S, Perez LF, Otero-Anton E, Gude F, Barrio E. Serum cytokines and increased total serum IgE in alcoholics. *Ann Allergy Asthma Immunol*. 1999; 83:61–7. [PubMed: 10437818]
171. Horiguchi N, Ishac EJ, Gao B. Liver regeneration is suppressed in alcoholic cirrhosis: correlation with decreased STAT3 activation. *Alcohol*. 2007; 41:271–80. [PubMed: 17630087]
172. Carmiel-Haggai M, Cederbaum AI, Nieto N. Binge ethanol exposure increases liver injury in obese rats. *Gastroenterology*. 2003; 125:1818–33. [PubMed: 14724834]
173. Yu S, Rao S, Reddy JK. Peroxisome proliferator-activated receptors, fatty acid oxidation, steatohepatitis and hepatocarcinogenesis. *Curr Mol Med*. 2003; 3:561–72. [PubMed: 14527087]
174. Kliewer SA, Forman BM, Blumberg B, Ong ES, Borgmeyer U, Mangelsdorf DJ, Umesono K, Evans RM. Differential expression and activation of a family of murine peroxisome proliferator-activated receptors. *Proc Natl Acad Sci USA*. 1994; 91:7355–9. [PubMed: 8041794]
175. Lee SS, Pineau T, Drago J, Lee EJ, Owens JW, Kroetz DL, Fernandez-Salguero PM, Westphal H, Gonzalez FJ. Targeted disruption of the α isoform of the peroxisome proliferator-activated receptor gene in mice results in abolishment of the pleiotropic effects of peroxisome proliferators. *Mol Cell Biol*. 1995; 15:3012–22. [PubMed: 7539101]
176. Palmer CN, Hsu MH, Griffin KJ, Raucy JL, Johnson EF. Peroxisome proliferator activated receptor- α expression in human liver. *Mol Pharmacol*. 1998; 53:14–22. [PubMed: 9443928]
177. Costet P, Legendre C, More J, Edgar A, Galtier P, Pineau T. Peroxisome proliferator-activated receptor α -isoform deficiency leads to progressive dyslipidemia with sexually dimorphic obesity and steatosis. *J Biol Chem*. 1998; 273:29577–85. [PubMed: 9792666]

178. Kersten S, Seydoux J, Peters JM, Gonzalez FJ, Desvergne B, Wahli W. Peroxisome proliferator-activated receptor α mediates the adaptive response to fasting. *J Clin Invest.* 1999; 103:1489–98. [PubMed: 10359558]
179. Leone TC, Weinheimer CJ, Kelly DP. A critical role for the peroxisome proliferator-activated receptor α (PPAR α) in the cellular fasting response: the PPAR α -null mouse as a model of fatty acid oxidation disorders. *Proc Natl Acad Sci USA.* 1999; 96:7473–8. [PubMed: 10377439]
180. Canaple L, Rambaud J, Dkhissi-Benyahya O, Rayet B, Tan NS, Michalik L, Delaunay F, Wahli W, Laudet V. Reciprocal regulation of brain and muscle Arnt-like protein 1 and peroxisome proliferator-activated receptor α defines a novel positive feedback loop in the rodent liver circadian clock. *Mol Endocrinol.* 2006; 20:1715–27. [PubMed: 16556735]
181. Yang X, Zhang YK, Esterly N, Klaassen CD, Wan YJ. Gender disparity of hepatic lipid homeostasis regulated by the circadian clock. *J Biochem.* 2009; 145:609–23. [PubMed: 19174548]
182. Gibbons GF, Patel D, Wiggins D, Knight BL. The functional efficiency of lipogenic and cholesterologenic gene expression in normal mice and in mice lacking the peroxisomal proliferator-activated receptor- α (PPAR- α). *Adv Enzyme Regul.* 2002; 42:227–47. [PubMed: 12123718]
183. Patel DD, Knight BL, Wiggins D, Humphreys SM, Gibbons GF. Disturbances in the normal regulation of SREBP-sensitive genes in PPAR α -deficient mice. *J Lipid Res.* 2001; 42:328–37. [PubMed: 11254743]
184. Nanji AA, Dannenberg AJ, Jokelainen K, Bass NM. Alcoholic liver injury in the rat is associated with reduced expression of peroxisome proliferator- α (PPAR α)-regulated genes and is ameliorated by PPAR α activation. *J Pharmacol Exp Ther.* 2004; 310:417–24. [PubMed: 15016835]
185. Wan YJ, Morimoto M, Thurman RG, Bojes HK, French SW. Expression of the peroxisome proliferator-activated receptor gene is decreased in experimental alcoholic liver disease. *Life Sci.* 1995; 56:307–17. [PubMed: 7837930]
186. Wada S, Yamazaki T, Kawano Y, Miura S, Ezaki O. Fish oil fed prior to ethanol administration prevents acute ethanol-induced fatty liver in mice. *J Hepatol.* 2008; 49:441–50. [PubMed: 18620774]
187. Dohmen K, Wen CY, Nagaoka S, Yano K, Abiru S, Ueki T, Komori A, Daikoku M, Yatsushashi H, Ishibashi H. Fenofibrate-induced liver injury. *World J Gastroenterol.* 2005; 11:7702–3. [PubMed: 16437706]
188. Gariot P, Barrat E, Mejean L, Pointel JP, Drouin P, Debry G. Fenofibrate and human liver. Lack of proliferation of peroxisomes. *Arch Toxicol.* 1983; 53:151–63. [PubMed: 6882216]
189. Gyamfi MA, Wan YJ. Mechanisms of resistance of hepatocyte retinoid X receptor α -null mice to WY-14,643-induced hepatocyte proliferation and cholestasis. *J Biol Chem.* 2009; 284:9321–30. [PubMed: 19176532]
190. Lucena MI, Andrade RJ, Vicioso L, Gonzalez FJ, Pachkoria K, Garcia-Munoz B. Prolonged cholestasis after raloxifene and fenofibrate interaction: A case report. *World J Gastroenterol.* 2006; 12:5244–6. [PubMed: 16937543]
191. Obourn JD, Frame SR, Bell RH Jr, Longnecker DS, Elliott GS, Cook JC. Mechanisms for the pancreatic oncogenic effects of the peroxisome proliferator Wyeth-14,643. *Toxicol Appl Pharmacol.* 1997; 145:425–36. [PubMed: 9266817]
192. Galli A, Pinaire J, Fischer M, Dorris R, Crabb DW. The transcriptional and DNA binding activity of peroxisome proliferator-activated receptor α is inhibited by ethanol metabolism. A novel mechanism for the development of ethanol-induced fatty liver. *J Biol Chem.* 2001; 276:68–75. [PubMed: 11022051]
193. Tuma DJ, Hoffman T, Sorrell MF. The chemistry of acetaldehyde–protein adducts. *Alcohol Alcohol.* 1991; 1(Suppl 1):271–6.
194. Devchand PR, Keller H, Peters JM, Vazquez M, Gonzalez FJ, Wahli W. The PPAR α -leukotriene B4 pathway to inflammation control. *Nature.* 1996; 384:39–43. [PubMed: 8900274]
195. Blok WL, Katan MB, van der Meer JW. Modulation of inflammation and cytokine production by dietary (*n*-3) fatty acids. *J Nutr.* 1996; 126:1515–33. [PubMed: 8648424]

196. Whelan J. Antagonistic effects of dietary arachidonic acid and *n*-3 polyunsaturated fatty acids. *J Nutr.* 1996; 126:1086S–91S. [PubMed: 8642438]
197. Delerive P, De K, Besnard S, Vanden Berghe W, Peters JM, Gonzalez FJ, Fruchart JC, Tedgui A, Haegeman G, Staels B. Peroxisome proliferator-activated receptor α negatively regulates the vascular inflammatory gene response by negative cross-talk with transcription factors NF- κ B and AP-1. *J Biol Chem.* 1999; 274:32048–54. [PubMed: 10542237]
198. Wang N, Verna L, Chen NG, Chen J, Li H, Forman BM, Stemberman MB. Constitutive activation of peroxisome proliferator-activated receptor- γ suppresses pro-inflammatory adhesion molecules in human vascular endothelial cells. *J Biol Chem.* 2002; 277:34176–81. [PubMed: 12107164]
199. Delerive P, Gervois P, Fruchart JC, Staels B. Induction of IkappaB α expression as a mechanism contributing to the anti-inflammatory activities of peroxisome proliferator-activated receptor- α activators. *J Biol Chem.* 2000; 275:36703–7. [PubMed: 10980195]
200. Kleemann R, Gervois PP, Verschuren L, Staels B, Princen HM, Kooistra T. Fibrates down-regulate IL-1-stimulated C-reactive protein gene expression in hepatocytes by reducing nuclear p50-NF κ B-C/EBP- β complex formation. *Blood.* 2003; 101:545–51. [PubMed: 12393563]
201. Spiegelman BM. PPAR- γ : adipogenic regulator and thiazolidinedione receptor. *Diabetes.* 1998; 47:507–14. [PubMed: 9568680]
202. Kliewer SA, Willson TM. The nuclear receptor PPAR γ —bigger than fat. *Curr Opin Genet Dev.* 1998; 8:576–81. [PubMed: 9794815]
203. Desreumaux P, Dubuquoy L, Nutten S, Peuchmaur M, Englaro W, Schoonjans K, Derijard B, Desvergne B, Wahli W, Chambon P, Leibowitz MD, Colombel JF, Auwerx J. Attenuation of colon inflammation through activators of the retinoid X receptor (RXR)/ peroxisome proliferator-activated receptor γ (PPAR γ) heterodimer. A basis for new therapeutic strategies. *J Exp Med.* 2001; 193:827–38. [PubMed: 11283155]
204. Ricote M, Li AC, Willson TM, Kelly CJ, Glass CK. The peroxisome proliferator-activated receptor- γ is a negative regulator of macrophage activation. *Nature.* 1998; 391:79–82. [PubMed: 9422508]
205. Uchimura K, Nakamuta M, Enjoji M, Irie T, Sugimoto R, Muta T, Iwamoto H, Nawata H. Activation of retinoic X receptor and peroxisome proliferator-activated receptor- γ inhibits nitric oxide and tumor necrosis factor- α production in rat Kupffer cells. *Hepatology.* 2001; 33:91–9. [PubMed: 11124825]
206. Ahima RS, Flier JS. Leptin. *Annu Rev Physiol.* 2000; 62:413–37. [PubMed: 10845097]
207. Memon RA, Tecott LH, Nonogaki K, Beigneux A, Moser AH, Grunfeld C, Feingold KR. Up-regulation of peroxisome proliferator-activated receptors (PPAR- α) and PPAR- γ messenger ribonucleic acid expression in the liver in murine obesity: troglitazone induces expression of PPAR- γ -responsive adipose tissue-specific genes in the liver of obese diabetic mice. *Endocrinology.* 2000; 141:4021–31. [PubMed: 11089532]
208. Podrez EA, Febbraio M, Sheibani N, Schmitt D, Silverstein RL, Hajjar DP, Cohen PA, Frazier WA, Hoff HF, Hazen SL. Macrophage scavenger receptor CD36 is the major receptor for LDL modified by monocyte-generated reactive nitrogen species. *J Clin Invest.* 2000; 105:1095–108. [PubMed: 10772654]
209. Boelsterli UA, Bedoucha M. Toxicological consequences of altered peroxisome proliferator-activated receptor γ (PPAR γ) expression in the liver: insights from models of obesity and type 2 diabetes. *Biochem Pharmacol.* 2002; 63:1–10. [PubMed: 11754868]
210. Greiffenstein P, Mathis KW, Stouwe CV, Molina PE. Alcohol binge before trauma/hemorrhage impairs integrity of host defense mechanisms during recovery. *Alcohol Clin Exp Res.* 2007; 31:704–15. [PubMed: 17374050]
211. Enomoto N, Takei Y, Hirose M, Konno A, Shibuya T, Matsuyama S, Suzuki S, Kitamura KI, Sato N. Prevention of ethanol-induced liver injury in rats by an agonist of peroxisome proliferator-activated receptor- γ , pioglitazone. *J Pharmacol Exp Ther.* 2003; 306:846–54. [PubMed: 12805475]
212. St-Pierre J, Drori S, Uldry M, Silvaggi JM, Rhee J, Jager S, Handschin C, Zheng K, Lin J, Yang W, Simon DK, Bachoo R, Spiegelman BM. Suppression of reactive oxygen species and

- neurodegeneration by the PGC-1 transcriptional coactivators. *Cell*. 2006; 127:397–408. [PubMed: 17055439]
213. Valle I, Alvarez-Barrientos A, Arza E, Lamas S, Monsalve M. PGC-1 α regulates the mitochondrial antioxidant defense system in vascular endothelial cells. *Cardiovasc Res*. 2005; 66:562–73. [PubMed: 15914121]
 214. Castrillo A, Joseph SB, Marathe C, Mangelsdorf DJ, Tontonoz P. Liver X receptor-dependent repression of matrix metalloproteinase-9 expression in macrophages. *J Biol Chem*. 2003; 278:10443–9. [PubMed: 12531895]
 215. Joseph SB, Castrillo A, Laffitte BA, Mangelsdorf DJ, Tontonoz P. Reciprocal regulation of inflammation and lipid metabolism by liver X receptors. *Nat Med*. 2003; 9:213–9. [PubMed: 12524534]
 216. Kalaany NY, Mangelsdorf DJ. LXRS and FXR: the yin and yang of cholesterol and fat metabolism. *Annu Rev Physiol*. 2006; 68:159–91. [PubMed: 16460270]
 217. Repa JJ, Liang G, Ou J, Bashmakov Y, Lobaccaro JM, Shimomura I, Shan B, Brown MS, Goldstein JL, Mangelsdorf DJ. Regulation of mouse sterol regulatory element-binding protein-1c gene (SREBP-1c) by oxysterol receptors, LXR α and LXR β . *Genes Dev*. 2000; 14:2819–30. [PubMed: 11090130]
 218. Joseph SB, Laffitte BA, Patel PH, Watson MA, Matsukuma KE, Walczak R, Collins JL, Osborne TF, Tontonoz P. Direct and indirect mechanisms for regulation of fatty acid synthase gene expression by liver X receptors. *J Biol Chem*. 2002; 277:11019–25. [PubMed: 11790787]
 219. You M, Crabb DW. Molecular mechanisms of alcoholic fatty liver: role of sterol regulatory element-binding proteins. *Alcohol*. 2004; 34:39–43. [PubMed: 15670664]
 220. Shimano H, Horton JD, Hammer RE, Shimomura I, Brown MS, Goldstein JL. Overproduction of cholesterol and fatty acids causes massive liver enlargement in transgenic mice expressing truncated SREBP-1a. *J Clin Invest*. 1996; 98:1575–84. [PubMed: 8833906]
 221. Horton JD, Goldstein JL, Brown MS. SREBPs: activators of the complete program of cholesterol and fatty acid synthesis in the liver. *J Clin Invest*. 2002; 109:1125–31. [PubMed: 11994399]
 222. Bateson MC, Maclean D, Evans JR, Bouchier IA. Chenodeoxycholic acid therapy for hypertriglyceridaemia in men. *Br J Clin Pharmacol*. 1978; 5:249–54. [PubMed: 656270]
 223. Carulli N, Ponz de Leon M, Podda M, Zuin M, Strata A, Frigerio G, Digrisolo A. Chenodeoxycholic acid and ursodeoxycholic acid effects in endogenous hypertriglyceridemias. A controlled double-blind trial. *J Clin Pharmacol*. 1981; 21:436–42. [PubMed: 7031100]
 224. Kast HR, Nguyen CM, Sinal CJ, Jones SA, Laffitte BA, Reue K, Gonzalez FJ, Willson TM, Edwards PA. Farnesoid X-activated receptor induces apolipoprotein C-II transcription: a molecular mechanism linking plasma triglyceride levels to bile acids. *Mol Endocrinol*. 2001; 15:1720–8. [PubMed: 11579204]
 225. Watanabe M, Houten SM, Wang L, Moschetta A, Mangelsdorf DJ, Heyman RA, Moore DD, Auwerx J. Bile acids lower triglyceride levels via a pathway involving FXR, SHP, and SREBP-1c. *J Clin Invest*. 2004; 113:1408–18. [PubMed: 15146238]
 226. Pineda Torra I, Claudel T, Duval C, Kosykh V, Fruchart JC, Staels B. Bile acids induce the expression of the human peroxisome proliferator-activated receptor α gene via activation of the farnesoid X receptor. *Mol Endocrinol*. 2003; 17:259–72. [PubMed: 12554753]
 227. Sinal CJ, Tohkin M, Miyata M, Ward JM, Lambert G, Gonzalez FJ. Targeted disruption of the nuclear receptor FXR/BAR impairs bile acid and lipid homeostasis. *Cell*. 2000; 102:731–44. [PubMed: 11030617]
 228. Dhe-Paganon S, Duda K, Iwamoto M, Chi YI, Shoelson SE. Crystal structure of the HNF4 α ligand binding domain in complex with endogenous fatty acid ligand. *J Biol Chem*. 2002; 277:37973–6. [PubMed: 12193589]
 229. Wisely GB, Miller AB, Davis RG, Thornquest AD Jr, Johnson R, Spitzer T, Seftler A, Shearer B, Moore JT, Willson TM, Williams SP. Hepatocyte nuclear factor 4 is a transcription factor that constitutively binds fatty acids. *Structure*. 2002; 10:1225–34. [PubMed: 12220494]
 230. Hayhurst GP, Lee YH, Lambert G, Ward JM, Gonzalez FJ. Hepatocyte nuclear factor 4 α (nuclear receptor 2A1) is essential for maintenance of hepatic gene expression and lipid homeostasis. *Mol Cell Biol*. 2001; 21:1393–403. [PubMed: 11158324]

231. Tirona RG, Lee W, Leake BF, Lan LB, Cline CB, Lamba V, Parviz F, Duncan SA, Inoue Y, Gonzalez FJ, Schuetz EG, Kim RB. The orphan nuclear receptor HNF4 α determines PXR- and CAR-mediated xenobiotic induction of CYP3A4. *Nat Med.* 2003; 9:220–4. [PubMed: 12514743]
232. Volle DH, Repa JJ, Mazur A, Cummins CL, Val P, Henry-Berger J, Caira F, Veyssiere G, Mangelsdorf DJ, Lobaccaro JM. Regulation of the aldo–keto reductase gene *akr1b7* by the nuclear oxysterol receptor LXR α (liver X receptor- α) in the mouse intestine: putative role of LXRs in lipid detoxification processes. *Mol Endocrinol.* 2004; 18:888–98. [PubMed: 14739254]
233. Finn RD, Henderson CJ, Scott CL, Wolf CR. Unsaturated fatty acid regulation of cytochrome P450 expression via a CAR-dependent pathway. *Biochem J.* 2009; 417:43–54. [PubMed: 18778245]
234. Gao J, He J, Zhai Y, Wada T, Xie W. CAR is an anti-obesity nuclear receptor that improves insulin sensitivity. *J Biol Chem.* 2009; 284:25984–92. [PubMed: 19617349]
235. Guo D, Sarkar J, Suino-Powell K, Xu Y, Matsumoto K, Jia Y, Yu S, Khare S, Haldar K, Rao MS, Foreman JE, Monga SP, Peters JM, Xu HE, Reddy JK. Induction of nuclear translocation of constitutive androstane receptor by peroxisome proliferator-activated receptor α synthetic ligands in mouse liver. *J Biol Chem.* 2007; 282:36766–76. [PubMed: 17962186]
236. Wieneke N, Hirsch-Ernst KI, Kuna M, Kersten S, Puschel GP. PPAR α -dependent induction of the energy homeostasis-regulating nuclear receptor NR1 β 3 (CAR) in rat hepatocytes: potential role in starvation adaptation. *FEBS Lett.* 2007; 581:5617–26. [PubMed: 18023279]
237. Roth A, Looser R, Kaufmann M, Meyer UA. Sterol regulatory element binding protein 1 interacts with pregnane X receptor and constitutive androstane receptor and represses their target genes. *Pharmacogenet Genom.* 2008; 18:325–37.
238. Zhou J, Zhai Y, Mu Y, Gong H, Uppal H, Toma D, Ren S, Evans RM, Xie W. A novel pregnane X receptor-mediated and sterol regulatory element-binding protein-independent lipogenic pathway. *J Biol Chem.* 2006; 281:15013–20. [PubMed: 16556603]
239. Fisher CD, Jackson JP, Lickteig AJ, Augustine LM, Cherrington NJ. Drug metabolizing enzyme induction pathways in experimental non-alcoholic steatohepatitis. *Arch Toxicol.* 2008; 82:959–64. [PubMed: 18488193]
240. Roth A, Looser R, Kaufmann M, Blattler SM, Rencurel F, Huang W, Moore DD, Meyer UA. Regulatory cross-talk between drug metabolism and lipid homeostasis: constitutive androstane receptor and pregnane X receptor increase *Insig-1* expression. *Mol Pharmacol.* 2008; 73:1282–9. [PubMed: 18187584]
241. Wang K, Damjanov I, Wan YJ. The protective role of pregnane X receptor in lipopolysaccharide/D-galactosamine-induced acute liver injury. *Lab Invest.* 2010; 90:257–65. [PubMed: 19997066]
242. Hui Y, Yu-Yuan L, Yu-Qiang N, Wei-Hong S, Yan-Lei D, Xiao-Bo L, Yong-Jian Z. Effect of peroxisome proliferator-activated receptors- γ and co-activator-1 α genetic polymorphisms on plasma adiponectin levels and susceptibility of non-alcoholic fatty liver disease in Chinese people. *Liver Int.* 2008; 28:385–92. [PubMed: 17999673]

Figure 1.

Hepatocyte RXR α modulates ethanol metabolism. ADH catalyzes the conversion of ethanol to acetaldehyde, a potent toxicant that accounts for most of the toxic effects of ethanol. Acetaldehyde produced from ethanol is further converted to the non-toxic acetate by a mitochondrial ALDH2. Both steps are coupled with the reduction of NAD⁺ to NADH. Both ethanol and acetaldehyde can be metabolized by CYP2E1. CYP2E1 has been implicated as the source of free radicals generated by ethanol metabolism. Hepatocyte RXR α deficiency results in a significant increase in hepatic ADH activity. In addition, mitochondrial ALDH2 and cytosolic ALDH activity is reduced when hepatocyte RXR α is not expressed. Accordingly, hepatic acetaldehyde clearance is reduced due to the lack of hepatocyte RXR α . Furthermore, SAMe and glutathione levels as well as the expression of GCLC, GST and GPx genes are significantly reduced due to the lack of hepatocyte RXR α . ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; CYP2E1, cytochrome P450 2E1; GST, glutathione S transferase; GCLC, glutamate–cysteine ligase catalytic subunit; GPx-1, glutathione peroxidase 1; GNMT, glycine N-methyl transferase; MAT, methionine adenosyl transferase; AHCY, adenosylhomocysteinase; SAMe, S-adenosylmethionine; SAH, S-adenosylhomocysteine

Figure 2.

Interaction among nuclear receptors (NRs), alcohol and lipid homeostasis. Research on the role of nuclear receptors in ALD have focused mainly on PPARs. The hepatic RXR α levels are decreased by alcohol administration.^{150,151} Down-regulation of PPAR α expression and fatty liver are observed following ethanol administration.^{184,185} The activation of SREBP-1c by ethanol feeding is associated with increased expression of lipogenic genes as well as the accumulation of triglycerides.²¹⁹ The activation of SREBP-1c has been suggested to involve LXR.²¹⁸ FXR represses lipogenesis by interfering with the expression of SREBP-1c through SHP, which inhibits the activity of LXR.²²⁵ Ethanol increases the mRNA levels of PPAR γ isoforms and the expression level of down-stream target fatty-acid translocase (CD36).¹⁸⁶ Fatty acids can induce CAR expression.²³⁶ The activation of CAR suppresses lipogenesis by decreasing the active form of SREBP-1c.²³⁷ PPAR γ , CD36, SCD-1 and FAE are direct transcriptional targets of PXR.²³⁸ HNF4 α is central regulator of bile acid and lipid homeostasis genes.²³⁰ These complex interactions among NRs involved in lipid homeostasis determine fat accumulation in the liver. SREBP-1c, sterol regulatory element-binding protein-1c; PPAR α , peroxisome proliferator-activated receptors α ; CPT-1, carnitine palmitoyl transferase-1; ACC, acetyl-CoA carboxylase; FAS, fatty acid synthase; SCD, stearoyl CoA desaturase; FAE, fatty acid elongase; FXR, farnesoid x receptor, LXR, liver x receptor, PXR, pregnane x receptor; CAR, constitutive androstane receptor; RXR, retinoic x receptor; HNF4 α , hepatocyte nuclear factor 4 α