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TOPIC HIGHLIGHT

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Peroxisome proliferator-activated receptor α, a potential therapeutic target for alcoholic liver disease

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Abstract

Alcoholic liver injury represents a progressive process with a range of consequences including hepatic steatosis, steatohepatitis, liver fibrosis, cirrhosis, and hepatocellular carcinoma. Targeting key molecular regulators involved in the development of alcoholic liver injury may be of great value in the prevention of liver injury. Peroxisome proliferator-activated receptor α (PPARα) plays a pivotal role in modulation of hepatic lipid metabolism, oxidative stress, inflammatory response and fibrogenesis. As such, PPARα may be a potential therapeutic target for the treatment of alcoholic liver disease.

Key words: Alcoholic liver disease; Oxidative stress; Inflammation; Fibrosis; Peroxisome proliferator-activated receptor α

Core tip: Alcoholic liver disease (ALD) is among the most common chronic liver disease. Modulation of therapeutic genes could potentially provide a novel and more effective treatment option. In this paper, we summarized the potential therapeutic role of PPARα modulation and illustrated the mechanism of PPARα in modulation of hepatic lipid metabolism, oxidative stress, inflammatory response and fibrogenesis in alcoholic liver disease. It is identified that PPARα agonists may serve as an effective therapeutic strategy for ALD.

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INTRODUCTION

Long-term and heavy consumption of alcohol is a major risk factor for chronic liver disease. Alcoholic liver disease (ALD) constitutes the major share of alcohol-related morbidity and mortality[1]. More than 90% of individuals who consume excessive amount of alcohol may suffer from hepatic steatosis, 5%-15% of whom may develop fibrosis and cirrhosis, and a small portion of cirrhotic patients may develop hepatocellular carcinoma[2,3]. Accumulation of lipid products such as triglycerides in hepatocytes leads to lipid superoxidation and oxidative stress, further provoking hepatocellular apoptosis, hepatic inflammation and fibrogenesis. During these processes, inflammatory cytokines, mitochondrial perturbation, activation of hepatic stellate cells (HSCs), and activation of transforming growth factor beta (TGF-β) signaling have been reported to play important roles[4]. Targeting the key molecular regulators involved in the above processes may be promising in preventing ALD.

Peroxisome proliferator-activated receptor α (PPARα), a subtype of the PPAR superfamily, interacts with the retinoid X receptor to function as a transcription factor to induce the expression of a series of genes involved in fatty acid transport, mitochondrial fatty acid oxidation,

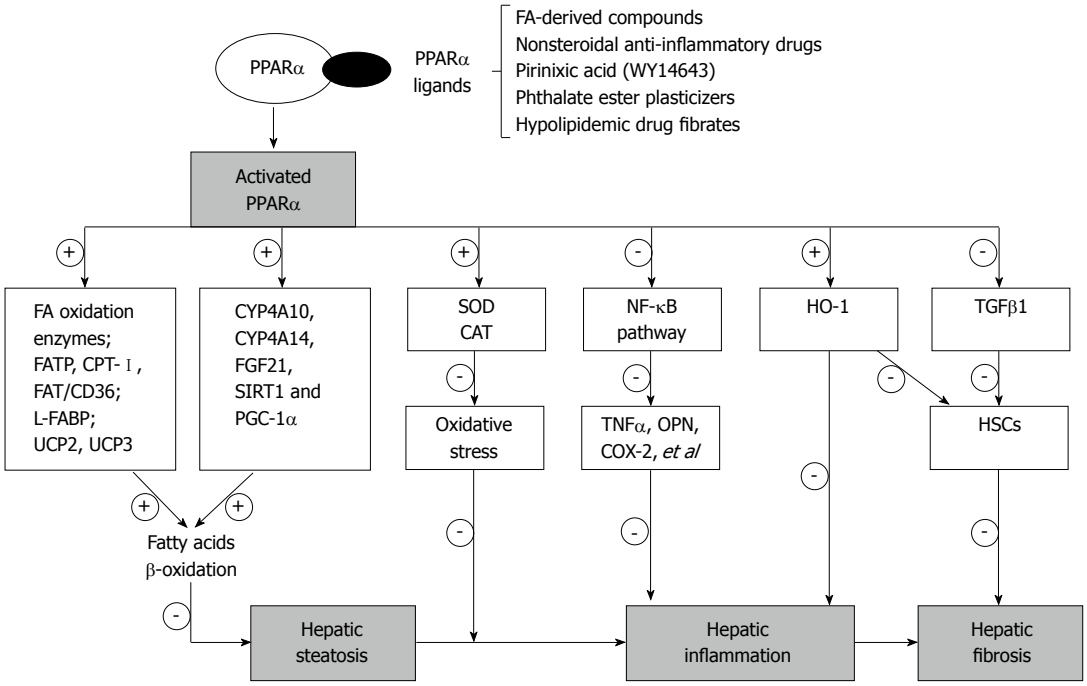

Figure 1 Protective role and partial mechanism of peroxisome proliferator-activated receptor α in alcoholic liver disease. Peroxisome proliferator-activated receptor α (PPARα) plays a critical role in modulation of hepatic lipid metabolism, oxidative stress, inflammatory response and fibrogenesis in alcoholic liver disease. Up-regulation of PPARα by its agonists (*e.g.*, fibrates, WY14643) leads to increased expression of fatty acid oxidation and transport enzymes, alleviated oxidative stress by increasing the expression of genes involved in antioxidant enzymes (*e.g.*, SOD and CAT), inhibited through activating nuclear factor kappa B (NF-κB) signal pathway and decreased fibrogenesis factors (*e.g.*, TGF-β1 and HSC activation). SOD: Superoxide dismutase; CAT: Catalase; TGF-β1: Transforming growth factor beta 1; HSCs: Hepatic stellate cells; COX-2: Cyclooxygenase-2; HO-1: Heme oxygenase-1; TNFα: Tumor necrosis factor α; OPN: Osteopontin.

catabolism, inflammatory response and fibrogenesis[5,6]. Many PPARα agonists (such as FA-derived compounds, carbaprostacyclin, nonsteroidal anti-inflammatory drugs, pirinixic acid, phthalate ester plasticizers, and hypolipidemic drug fibrates) have been evaluated for their therapeutic efficacy in animals or patients with ALD[7,8].

In this review, we focus on the protective role of PPARα in preventing hepatic injury induced by alcohol, and highlight the key signaling events mediating lipid metabolism, oxidative stress, hepatic inflammation and fibrosis in ALD (Figure 1).

REGULATORY ROLE OF PPARα IN LIPID METABOLISM IN ALD

Accumulation of fat (mainly triglycerides, phospholipids, and cholesterol esters) in hepatocytes is the first step of alcohol-induced liver injury. Impaired lipid metabolism, mainly increased glycerolipid synthesis and decreased fatty acid oxidation in hepatocytes, is the key mechanism leading to alcoholic liver injury. Alcohol dehydrogenase (ADH) is a key enzyme involved in the conversion of ethanol to acetaldehyde[9], which is then changed to acetate by acetaldehyde dehydrogenase (ALDH), the key mitochondrial enzyme oxidizing aldehyde into acetic acid without producing toxic effect to mitochondria. This process is associated with the reduction of NAD to nicotinamide adenine dinucleotide health (NADH). Increased NADH/NAD ratio inhibits fat acid metabolism through reduced fatty acid β-oxidation[10]. The acetaldehyde not only directly inhibits PPARα activity but also impairs the DNA-binding ability of PPARα[11-13]. Retinoic X receptor α (RXRα) is a heterodimeric partner required for high-affinity DNA binding by many nuclear receptors. An RXRα binding site in the promoter sequence of ALDH has been identified[14]. PPARα can increase or maintain RXRα expression in the liver, resulting in enhanced ALDH expression. This process decreases the level of hepatic aldehyde and prevents the liver injury[15,16].

The imbalance between lipid synthesis and fatty acid oxidation induces excessive fat accumulation in the liver, which plays a pivotal role in the progression of ALD[11]. It has been shown that some of the key enzymes of fatty acid oxidation are regulated by PPARα, including long-chain acyl-CoA dehydrogenase (LCAD), medium-chain acyl-CoA dehydrogenase (MCAD), acyl-CoA oxidase, and very-long-chain acyl-CoA synthetase (VLACS)[17]. PPARα also regulates fatty acid transport protein, carnitine palmitoyltransferase, fatty acid translocase/CD36, liver cytosolic fatty acid-binding protein (LFABP) and uncoupling protein-2 and 3 (UCP2 and UCP3)[18]. Ethanol metabolite acetaldehyde has been shown to suppress PPARα activity, resulting in decreased transcription of PPARα target genes, a subsequent increase in the synthesis of triglycerides and fatty acids, and a decrease in cellular fatty acid uptake and oxidation[19].

There has been much experimental evidence supporting the role of PPARα in regulating fatty acid metabo-

lism. PPARα ligands have been demonstrated to promote fatty acid oxidation and decrease fatty acid accumulation in experimental animals with ALD and such effects have been confirmed in ALD patients[20,21]. Hepatic mRNA expression of cytochrome P450 4A10 (CYP4A10) and CYP4A14, the characteristic PPARα target genes involved in fatty acid oxidation, could be restored by PPARα agonist WY14643[22]. In the experimental C57BL6/J mouse model of ALD (induced by Lieber-DeCarli liquid diet containing 4% ethanol), WY14643 administration could enhance the expression of hepatic fibroblast growth factor 21 and restore the hepatic expression of sirtuin 1 expression[23], which played a positive role in lipid metabolism, gluconeogenesis and fatty acid oxidation in the liver. Fischer *et al*[21] also found that WY14643 restored the ability of PPAR /RXR receptor complex to bind the specific response element, effectively upregulated the mRNAs expression of LCAD, acetyl-CoA carboxylase, MCAD, VLACS and LFABP, resulting in a higher rate of fatty acid oxidation, normalized serum free fatty acid and triacylglycerol levels, and prevented triacylglycerol accumulation in the liver of ethanol-fed mice.

PPARα SUPPRESSES ALCOHOL-INDUCED LIPID SUPEROXIDATION AND OXIDATIVE STRESS IN ALD

Oxidative stress is one of the key pathogenic factors involved in the development of necroinflammation and ultimately fibrosis and cirrhosis in ALD. Accumulation of fatty acids and generation of excessive amount of lipid peroxidation products can lead to oxidative stress, which in turn leads to mitochondrial dysfunction and enhanced hepatic expression of cytochrome P450 2E1 (CYP2E1)[24]. It is thought that induction of CYP2E1 by fatty acids is a major source of reactive oxygen species (ROS), which can strongly evoke oxidative stress and mitochondrial damage in hepatocytes. This can in turn affect fatty acid β-oxidation, cause hepatic steatosis, and produce necroinflammation[25]. The anti-oxidative effect of PPARα has been demonstrated by many published studies. PPAR-responsive elements (PPREs) have been identified in the promoter regions of several anti-oxidant genes such as catalase (CAT) and Cu^{2+}/Zn^{2+}-superoxide dismutase (SOD). PPARα can bind to PPREs to promote the expression of anti-oxidases, thereby inhibiting oxidative stress in the liver[26-29].

PPARα agonist WY14643 has been shown to prominently up-regulate the mRNA and protein expression of heme oxygenase-1 (HO-1, a stress-responsive protein that is induced by oxidants and plays an anti-oxidative role) in ethanol treated mice, and this was associated with alleviated oxidative stress, reduced lipid superoxidation and CYP2E1 expression[30]. On the other hand, lack of PPARα makes the liver more susceptible to alcohol induced injury. For example, compared with the wild-type mice, PPARα-null mice fed a Lieber-DeCarli diet containing 4% ethanol for 6 mo exhibited hepatomegaly, macrovesicular steatosis, hepatocyte apoptosis, mitochondrial swelling, hepatitis, and hepatic fibrosis[31]. Clearly, PPARα signaling forms a part of the body's defense mechanism and plays an important role in anti-oxidative stress in the liver.

PPARα AMELIORATES ALCOHOLIC HEPATITIS BY MODULATING INFLAMMATORY FACTORS

Alcoholic steatohepatitis (AH) is an important phase of ALD, characterized by inflammatory cell infiltration and hepatocellular injury. AH develops in patients with steatosis and is usually associated with progressive fibrosis. Lipid peroxidation and oxidative stress are important contributing factors for AH[32]. Ethanol consumption can induce penetration of lipopolysaccharides (LPS) from the gut to the liver where they can act as important cofactors for the progression of ALD[33]. LPS interacts with toll-like receptor 4 on macrophages/Kupffer cells, leading to increased secretion of pro-inflammatory cytokines such as tumor necrosis factor α (TNF-α), monocyte chemotactic protein 1, vascular cell adhesion molecule-1, and interleukin 6 (IL-6)[34]. In addition, LPS-induced activation of mitogen-activated protein kinases (MAPKs) also contributes to liver injury. Ethanol and its metabolites have also been shown to cause an up-regulation of pro-inflammatory factor osteopontin (OPN) and cyclooxygenase-2 (COX-2) in hepatocytes[35,36]. These factors further promote the synthesis of inflammatory mediators such as TNF-α and CXC chemokines (*e.g.*, IL-8) through activating nuclear factor kappa B (NF-κB), signal transducers and activators of transcription-Janus kinase, and Jun N-terminal kinase pathways in hepatic resident cells. Infiltration of parenchymal neutrophils in the liver is a prominent feature of AH. Many chemokines (*e.g.*, CXCL5, CXCL6 and CXCL4) and cytokines (*e.g.*, TNF-α, IL-1, IL-6 and OPN) are markedly up-regulated in response to alcohol consumption, and they in turn promote infiltration of neutrophils during progression of AH[37].

Studies have shown that PPARα exerts an anti-inflammatory role in ALD by negatively interfering with pro-inflammatory signaling pathway NF-κB and inhibiting the expression of the related inflammatory cytokines[38]. Induction of PPARα by WY14643 attenuated liver inflammatory response by repressing expression of pro-inflammatory cytokines phosphatidylinositol 3-kinase (PI3K), OPN and COX-2, as well as enhancing expression of anti-inflammatory factors adiponectin and HO-1[8]. PPARα could regulate HO-1 transcription directly by binding to a PPRE in the promoter region of HO-1[39]. Thus, up-regulation of PPARα may contribute to the amelioration of ethanol-induced hepatic inflammatory response.

PPARα REVERSES ETHANOL-INDUCED HEPATIC FIBROSIS BY INHIBITING ACTIVATION OF HEPATIC STELLATE CELLS AND EXPRESSION OF PRO-FIBROTIC GENES

Alcoholic liver fibrosis is a severe form of ALD. HSCs, the major source of extracellular matrix (ECM) in hepatic fibrosis, are also stimulated by ethanol metabolites such as acetaldehyde. Activation of HSCs is observed during alcoholic liver injury, resulting in their proliferation and hepatic fibrogenesis[40]. The role of HSC activation in liver fibrosis has been supported by many *in vitro* and *in vivo* studies. HSCs, damaged hepatocytes, activated Kupffer cells and infiltrating polymorphonuclear cells can all release fibrogenic mediators such as TGF-β1, visfatin and PI3K, and thereby promote collagen accumulation in ECM[41,42]. Meanwhile, activated TGF-β1 stimulates quiescent HSCs transdifferentiation into myofibroblast-like cells, which forms a positive feedback loop between fibrogenic cells and HSCs[43].

We have investigated the potential role of PPARα in inhibition of ethanol-induced liver fibrosis using a rodent model[23]. Up-regulation of hepatic pro-fibrogenic genes osteopontin, TGF-β1, visfatin, PI3K, matrix metalloproteinase-2 (MMP-2) and MMP-9 was observed in the mice fed a 4% ethanol-containing Lieber-DeCarli diet. Administration of WY14643 could restore the expression of those cytokines altered by ethanol treatment and concomitantly ameliorated the liver injury.

Pro-inflammatory cytokine TNF-α also plays a crucial role in the development of alcoholic liver fibrosis. TNF-α activates Kupffer cells through autocrine and paracrine pathways, and the activated Kupffer cells produce TNF-α, ROS and other inflammatory factors. These processes form a feedback mediation of progression from inflammation to fibrosis in ALD[44]. It has been suggested that WY14643 could prevent the fibrosis progression by dramatically decreasing the expression of TNF-α[23].

Accumulating evidence suggests that the imbalance between pro- and anti-inflammatory cytokines is an important factor in the pathogenesis of fibrosis in ALD. Among the inflammatory cytokines, IL-10 is a potent factor in the regulation of the expression of pro-fibrotic markers such as collagen I , TGF-β1 and MMP-9[45-47]. IL-10 also promotes apoptosis of activated HSCs by modulating the expression of pro-apoptotic genes Fas, Bax and anti-apoptosis gene Bcl-2[48]. In addition, IL-10 was found to up-regulate HO-1 expression through the p38 MAPK pathway[49]. To further support the role of IL-10 and PPARα in the liver fibrosis, PPARα agonist has been shown to prevent the progression of liver fibrosis by modulation of p38 MAPK phosphorylation[50], and hepatic IL-10 and HO-1 expression was up-regulated by PPARα agonist WY14643 in ethanol-fed mice[8].

CONCLUSION

ALD is among the most common chronic liver disease. Modulation of therapeutic genes could potentially provide a novel and more effective treatment option. PPARα might be a crucial target gene in the suppression of hepatic lipid synthesis and oxidative stress, and amelioration of hepatic inflammatory response and fibrosis. PPARα agonists may serve as an effective therapeutic strategy for ALD.

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