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Hepatic fibrosis: Targeting peroxisome proliferator-activated receptor alpha from mechanism to medicines

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Abstract

Liver fibrosis is the result of sustained chronic liver injury and inflammation leading to hepatocyte cell death followed by the formation of fibrous scars, which is the hallmark of NASH and alcoholic steatohepatitis and can lead to cirrhosis, HCC, and liver failure. Although progress has been made in understanding the pathogenesis and clinical consequences of hepatic fibrosis, therapeutic strategies for this disease are limited. Preclinical studies suggest that peroxisome proliferator-activated receptor alpha plays an important role in preventing the development of liver fibrosis by activating genes involved in detoxifying lipotoxicity and toxins, transrepressing genes involved in inflammation, and inhibiting activation of hepatic stellate cells. Given the robust preclinical data, several peroxisome proliferator-activated receptor alpha agonists have been tested in clinical trials for liver fibrosis. Here, we provide an update on recent progress in understanding the mechanisms by which peroxisome proliferator-activated receptor alpha prevents fibrosis and discuss the potential of targeting PPARα for the development of antifibrotic treatments.

INTRODUCTION

Hepatic fibrosis is the formation of fibrous scars that arise from sustained wound-healing response to chronic liver injury and inflammation originating from infectious, chemical-induced, cholestatic, and metabolic diseases.[1,2] Early-stage fibrosis is not a disease and causes no harm, but advanced fibrosis leads to cirrhosis, HCC, and liver failure and often requires liver transplantation. The clinical burden of hepatic fibrosis is not only confined

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to liver-related morbidity and mortality but also affects several extrahepatic organs and regulatory pathways.

Historically, hepatic fibrosis was thought to be a passive and irreversible process resulting from the substitution of hepatic parenchyma with a collagen-rich tissue.[3] However, some studies have demonstrated that even advanced hepatic fibrosis is potentially reversible,[4] and the removal of fibrogenic etiologies is effective in the treatment of hepatic fibrosis resulting from most chronic liver diseases.[5] Since the discovery of HSCs as collagen-producing cells in the liver,[6] key signals responsible for fibrosis have been delineated.[1,2] Although the primary signals that trigger fibrogenesis vary among etiologies, chronic inflammation is a common contributor to myofibroblastic activation that subsequently leads to production and secretion of extracellular matrix components such as collagen and fibronectin to form fibrous scaring.[1,2] It is now clear that activated HSCs are the major, but not the only, source of myofibroblasts.[7] For instance, hepatic myofibroblasts can be formed from portal fibroblasts and mesothelial cells in the presence of the fibrogenic cytokine TGF-β1.[8] Intriguingly, by ectopic expression of specific transcription factors, fibrogenic myofibroblasts can be reprogrammed into hepatocyte-like cells in mice.[9,10] All these pieces of evidence suggest that hepatic fibrosis is a reversible condition.

Steady progress in understanding the pathogenesis of hepatic fibrosis has revealed strategies and therapeutic targets for reversing fibrosis.[5] Preclinical studies suggest that peroxisome proliferator-activated receptor alpha (PPARα, NR1C1) is a potential therapeutic target.[11,12] Notably, the PPARα/γ dual agonist saroglitazar was licensed for the treatment of NASH in India,[13] which is the only approved drug for the treatment of fibrosis. Other PPARα agonists such as fenofibrate and bezafibrate are approved for the treatment of dyslipidemia.[12,14] In this review, we provide an update on recent progress into the mechanisms by which PPARα prevents liver fibrosis and discuss the potential of targeting PPARα for the development of antifibrotic treatments.

PPARα

PPARα along with PPARδ (or PPARβ, NR1C2) and PPARγ (NR1C3) are the 3 PPAR ligand-inducible transcription factors in the nuclear receptor superfamily. The tissue distributions of the 3 PPARs are different with PPARα abundantly expressed in the metabolic active tissues such as the liver, heart, kidneys, and the intestine, while PPARδ is more ubiquitously expressed, and PPARγ is predominantly found in the adipose tissue and immune cells.[15] Functionally, PPARα plays a critical role in hepatic lipid metabolism; PPARδ regulates lipid metabolism, mitochondrial respiration, and thermogenesis; and PPARγ is essential for the formation of adipose tissue and liver.[16]

The 3-dimensional structure of PPARs consists of a DNA-binding domain in the N-terminus and a ligand-binding domain in the C-terminus.[17] Both DNA-binding domain and ligand-binding domain are the most highly conserved regions across the 3 receptor forms.[18] The DNA-binding domain contains 2 zinc finger motifs that can specifically bind peroxisome proliferator response elements (PPREs), a DNA sequence with AGGTCA repeats separated by a single alternative nucleotide (AGGTCA-n-AGGTCA).[19] The ligand-binding domain has an extensive secondary structure comprising 13 α-helices and a small 4-stranded

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β-sheet.[19] Both natural and synthetic ligands can bind to the ligand-binding domain,[20] and after interaction with specific ligands, PPARs heterodimerize with retinoid X receptor (RXR) and bind to PPREs in the promoter region of target genes to activate transcription of gene batteries involved in normal cellular physiology as well as disease.[18] Notably, in addition to the modulation of gene transcription using PPREs, PPARs were found to repress other transcription factor pathways in a DNA-binding-independent manner.[21] For example, PPARα activation can suppress cytokine IL-1β-induced upregulation of many proinflammatory genes by interfering with NF-κB signaling.[22]

PPARα is the first member of the PPAR family identified in 1990 and is named based on the ability of its agonists, hypolipidemic drugs, or other compounds to induce peroxisome proliferation in rodents.[23] Peroxisomes are membrane-enclosed organelles that contain a complex set of enzymes involved in a variety of metabolic reactions, including the β-oxidation of fatty acids and metabolism of bile acids and cholesterol.[24] Consistently, the target genes of PPARα also play a key role in a plethora of lipid metabolic pathways, including (peroxisomal, microsomal, and mitochondrial) fatty acid oxidation, fatty acid elongation and desaturation, fatty acid binding and transport, triglyceride synthesis and breakdown, lipoprotein metabolism, bile acid metabolism, gluconeogenesis, and various other metabolic pathways.[25,26] As new evidence continues to emerge, the function of PPARα has expanded from being a master regulator of lipid metabolism to multiple aspects, such as modulating liver detoxification processes, suppressing inflammation, and reshaping the immune system.[27]

ROLES AND MECHANISMS FOR PPARα IN PREVENTING LIVER INJURY

Hepatocyte ballooning and multiple forms of hepatocyte death derived from liver injury contribute to the development of liver fibrosis.[28] Through releasing a wide range of signals, injured hepatocytes subsequently trigger inflammation, HSC activation, and fibrogenesis.[28] Since chronic viral infections, alcohol abuse, cholestasis, and metabolic syndrome are the major causative agents leading to liver injury,[1] and current evidence suggests that PPARα is involved in all these injuries through different mechanisms, this section summarizes the potential roles and mechanisms by which PPARα prevents liver injuries in subsections according to different causative agents.

PPARα is involved in virus-induced hepatocellular injury—Chronic HBV/HCV infection represents a major global health problem that can lead to liver fibrosis and cirrhosis.[29,30] The mechanism for this fibrosis is primarily attributed to immune deregulations,[29] but current studies have illustrated that HBV or HCV infection suppresses hepatic PPARα expression and transcriptional activity.[31–33] Mechanisms accounting for this effect include upregulation of microRNA-27 (miR-27) or miR-200c by HCV[33,34] or formation of a complex between HBV X-associated protein 2 (XAP2) and PPARα.[35] In contrast, activation of PPARα and the resultant lipolysis improved HCV-induced liver lesions,[36,37] the PPARα L162V polymorphism tended to favor HBV-induced HCC,[38] and PPARα transrepressive activity on inflammation-repressed HCV entry into hepatocytes.[39] Although these pieces of evidence suggest that PPARα activation may be involved in

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preventing virus-induced hepatocellular injury, detailed mechanistic studies remain to be explored.

PPARα prevents chemical-induced hepatocellular injury—Hepatocellular injury may stem from a broad range of chemical toxins including ethanol, drugs, and other organic or inorganic toxins. Among them, alcohol consumption is a major risk factor for chronic liver diseases.[40]

Ethanol can cause hepatocellular injury through a variety of mechanisms. Due to its high energy density and easy availability, ethanol is an important energy source, but it also facilities hepatic fat accumulation through increasing fatty acid synthesis and suppressing fatty acid oxidation, gluconeogenesis, and tricarboxylic acid cycle.[41,42] Under this condition, free fatty acids can promote hepatic lipotoxicity that contributes to the pathogenesis of advanced liver diseases.[43] But a liver injury is not simply caused by hepatic fat accumulation.[44] Growing evidence suggests ethanol as a true hepatic toxin,[45] which leads to the formation of hepatic lesions derived from either ethanol metabolism or ethanol-induced leakage of gut endotoxins.[42,46] In hepatocytes, ethanol is primarily oxidized into acetaldehyde by cytosolic alcohol dehydrogenase, microsomal cytochromes P450 (CYPs), and peroxisomal catalase,[47] and acetaldehyde is rapidly metabolized to acetic acid or acetate by aldehyde dehydrogenase (Figure 1).[47] The metabolite acetaldehyde and CYP2E1-generated reactive oxygen species (ROS) are molecules that can easily react with macromolecules including lipid, protein, RNA, and DNA to promote oxidative stress, lipid peroxidation, hepatocellular damage, and mitochondrial dysfunction.[45,48] Given that acetaldehyde is rapidly detoxified by aldehyde dehydrogenase [47] and the expression of CYP2E1 increases from 4- up to 10-fold after alcohol consumption,[49,50] liver injury may predominantly stem from ROS rather than acetaldehyde. Consistent with this view, ethanol-induced oxidative stress and liver injury in mice are decreased in mice lacking CYP2E1 but restored in *CYP2E1*-humanized mice,[45] which suggests that CYP2E1-induced oxidative stress is necessary and sufficient to orchestrate liver injury in ethanol-treated mice. In addition, during ethanol metabolism, large amounts of NAD^+ are converted to its reduced form NADH,[40] which in turn activates pyruvate dehydrogenase kinase and as a result prevents glucose disposal by inhibiting the pyruvate dehydrogenase complex,[51] which may exacerbate insulin resistance,[52] especially under conditions of lipotoxicity.[43] Taken together, lipotoxicity and oxidative stress may be the root cause of ethanol-induced hepatic lesions attributing to alcoholic liver disease.[53]

PPARα activation plays a central role in detoxifying free fatty acid by transcriptionally modulating the expression of most key genes involved in fatty acid catabolism[25,26] and in defense against oxidative stress by increasing the expression of antioxidant enzymes including catalase[54,55] and CuZn-superoxide dismutase (SOD1) (Figure 1).[56] Furthermore, given that *Aldh* is a target gene of RXRα[57] that is stabilized by PPARα,[58] the indirect upregulation of *Aldh* by activated PPARα facilitates acetaldehyde removal.[57,59] Therefore, it is proposed that PPARα acts as an initial and central regulator of ethanol-induced hepatocellular injury (Box 1, Figure 1).[53] Consistent with this concept, it was reported that ethanol metabolism might inactivate PPARα, which arises from either acetaldehyde-mediated direct inhibition of the transcriptional and DNA-binding

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activity of PPARα, [60] or ROS and adenosine-mediated indirect inhibition of PPARα activity by suppressing adiponectin and zinc, respectively,[62–64] or microRNAs such as miR-155-mediated inhibition of PPARα translation,[65] or CYP2E1-induced metabolism of endogenous PPARα ligands.[71] Although it is not yet clear whether inactivation of PPARα exacerbates or triggers ethanol-induced oxidative stress and lipotoxicity,[42,45,72] PPARα activation completely switched alcohol metabolism from the CYP2E1 pathway to the catalase pathway along with suppressed ROS production and accelerated alcohol clearance (Figure 1).[66] Moreover, there is increasing evidence that ethanol diet-fed *Ppara*-null mice developed more severe liver steatosis and injury,[67,68] whereas upregulation of PPARα by inhibiting its upstream microRNAs abrogated ethanol-induced liver lesions.[65] Activation of PPARα by synthetic or endogenous ligands prevented ethanol-induced liver injury.[68–70] Therefore, PPARα might be a potential target for the detoxification of ethanol hepatotoxicity, thereby preventing the progression of alcoholic liver disease.

In other chemical liver fibrosis models, PPARα activation also serves as a mechanism to prevent hepatocellular toxicity. For example, carbon tetrachloride (CCl_4), a widely used chemical in experimental models to induce liver fibrosis,[73] was reported to suppress the expression and activity of PPARα.[74,75] Although CCl_4-induced liver injury might be associated with multiple biological processes, pathways, and targets,[76] several PPARα agonists ameliorated hepatocellular injury induced by CCl_4 alone or combined with other agents,[70,77] and the activation of PPARα also mediated the protective role of melatonin,[75] 4’-O-methylhonokiol,[78] and apigenin[79] in CCl_4-induced liver injury. Similar beneficial effects of PPARα on attenuating liver injury were also reported in fibrosis models induced by other chemicals including acetaminophen,[80,81] alpha-naphthyl isothiocyanate,[82] and thioacetamide.[55] At least 2 potential mechanisms mediate the benefits of PPARα. One mechanism is to increase drug detoxification by upregulating its target drug-metabolizing enzymes including CYP2C8 and CYP3A4.[83,84] Another mechanism may be attributed to the upregulation of antioxidant enzymes,[54–56] thereby preventing oxidative stress that accounts for the hepatotoxicity of all these chemicals.[85–88] Collectively, PPARα activation enhances antioxidant capacity and the detoxification of chemical toxins by CYPs, which may prevent hepatocellular injury and their detrimental effects on hepatic inflammation and fibrosis.

PPARα attenuates lipotoxicity in NAFLD—NAFLD is the most prevalent liver disease worldwide affecting ~1-quarter of the global adult population.[89] Steatosis is the initial stage of this disease, which can progress to NASH, liver fibrosis, liver cirrhosis, and HCC. While detailed mechanisms for progression from steatosis to the more aggressive NASH disorder remain to be fully explored, available data underscore the central role of lipid metabolism dysregulationand lipotoxicity as initiators of hepatocellular lesions and fibrosis.[90,91]

Growing evidence has implicated PPARα activation in preventing fat accumulation and the resultant lipotoxicity and injury (Box 2). Epidemiologic data revealed a negative correlation of hepatic PPARα expression with the severity of steatosis, NASH, and fibrosis,[92] and the single-nucleotide polymorphisms of PPARα (L162V) predispose individuals to the development and progression of NAFLD.[97] *Ppara*-null mice spontaneously develop

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hypercholesterolemia and steatosis[94] and have substantially exacerbated fasting-induced elevation of hepatic free fatty acids and liver injury.[95,96] Similarly, hepatocyte-specific PPARα knockout mice fed a standard diet developed NAFLD in old age[98] and promoted high-fat diet-induced liver lesions,[99] suggesting that liver PPARα is crucial for whole-body lipid homeostasis and is a potential therapeutic target for hepatocellular injury and NAFLD.[98]

The primary protective role of PPARα against lipotoxicity may arise from its function as a nuclear receptor. It is now clear that a wide range of fatty acids and their derivatives are endogenous PPARα ligands,[93] and many of these ligands activate PPARα within a nanomolar range.[100] This supports the concept that PPARα serves as an intracellular metabolic sensor[101] and fatty acid sensor.[26,27] When certain fatty acids or their metabolic intermediates are present, PPARα will be activated and direct the oxidative degradation of these molecules by controlling gene transcription of enzymes required for lipid catabolism.[26] Currently, PPARα target genes cover almost all lipid metabolic processes,[26] and functional PPREs were identified in the promoters of genes encoding rate-limiting enzymes for fatty acid oxidation, such as CYP4A in microsomal ω-oxidation,[102,103] acyl-CoA oxidase 1 in peroxisomal β-oxidation,[104] and acyl-CoA dehydrogenase medium chain in mitochondrial β-oxidation.[105] Moreover, PPARα transactivates antioxidant enzymes[54–56] and transrepresses inflammation,[21] which further facilitates its function to counteract fibrosis. Consequently, some studies have suggested PPARα as a potential target to develop hypolipidemic and antifibrotic drugs.[106,107]

PPARα suppresses cholestatic liver injury—Cholestasis is a pathologic condition characterized by a decrease in bile flow resulting from impaired bile acid synthesis or obstructed bile acid transport and excretion inside or outside the liver.[108,109] Owing to hydrophobic bile acids being highly toxic when accumulated at high concentrations in hepatocytes,[110] chronic cholestasis contributes to the development of hepatic fibrosis and cirrhosis.[109,111] While cholestatic liver fibrosis may arise from genetic defects, mechanical injury of the bile ducts, and dysregulation of immune responses,[1,112] its molecular mechanisms remain elusive. Growing evidence suggested that the nuclear receptors farnesoid X receptor (FXR, NR1H4) and PPARα coordinately control bile acid homeostasis by regulating the transcription of key proteins involved in bile acid biosynthesis and transport.[113–115] FXR and PPARα should have a central role in the pathogenesis of cholestatic hepatocellular injury and liver fibrosis (Box 3, Figure 2).

Through inhibiting the rate-limiting enzymes cholesterol 7α-hydroxylase (CYP7A1) and cytochrome sterol 27-hydroxylase (CYP27A1), the FXR-PPARα axis serves as a negative feedback mechanism to suppress bile acid synthesis (Figure 2).[114,131] Since FXR is a bile acid sensor[132] and PPARα is an FXR target[113] and lipid sensor,[25] the tight regulation of bile acid synthesis enzymes by the FXR-PPARα axis may act as a mechanism to ensure an optimal supply of bile acids in an ever-changing metabolic environment.[133,134] For example, activation of FXR by bile acids (when in excess) suppresses *Cyp7a1* transcription through PPARα or other nuclear receptors such as the small heterodimer partner (SHP, NROB2).[115,135] Activation of PPARα by agonists decreased Cyp7a1 mRNA expression and CYP7A1 enzyme activity by about 60%,[118,136] resulting from

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either PPARα-dependent direct repression of *Cyp7a1* transcription as both human and rat *Cyp7a1* promoter reporter activities were repressed by activated PPARα,[137,138] or PPARα-dependent decrease in cellular levels of hepatocyte nuclear factor 4α (HNF4α; NR2A1), a positive regulator of *Cyp7a1* transcription.[139,140] Fibrates and the PPARα ligand Wy-14,643 also suppressed CYP27A1 mRNA expression and enzyme activity.[118] Notably, *Pparα*-null mice do not have altered basal CYP7A1 and CYP27A1 levels as compared with wild-type mice,[118,141] but the repressive effect of fibrates on *Cyp7a1* and *Cyp27a1* transcription was completely abolished,[118,141] which indicates that it is the activation rather than the expression of PPARα that represses *Cyp7a1* and *Cyp27a1* transcription. In contrast, PPARα agonists increased the expression and activity of CYP8B1 and elevated the ratio of cholic acid to chenodeoxycholic acid.[114,126] All these effects were reversed in *Pparα*-null mice.[114,126] ChIP-seq data (GSE61817) showed that PPARα had a binding peak at the *Cyp8b1* promoter,[142] indicating a direct transcriptional activation of *Cyp8b1* by PPARα. This increase in CYP8B1 activity might play a compensatory role in maintaining cholic acid levels,[143] which did not change the effects of PPARα activation on the suppression of overall bile acid synthesis.[143] Consistently, evidence from healthy individuals[116] and primary biliary cirrhosis (PBC) or primary sclerosing cholangitis patients[117] showed that treatment with the PPARα agonist fenofibrate reduced serum bile acid concentrations.

In addition to decreasing bile acid synthesis, activation of PPARα also reduces hepatic bile acid accumulation and toxicity by promoting efflux and suppressing reuptake (Figure 2). After synthesis, bile acids are conjugated and amidated with taurine or glycine to form bile salts, which increase the hydrophilicity of bile acids. Then bile salts, together with phospholipids and cholesterol, are transported from hepatocytes into canaliculi by export pumps, largely by a series of ATP-binding cassette transport proteins (ABCs) including ABCB11/BSEP,[144] ABCB4 (also known as MDR3 in humans or MDR2 in mice),[145] and ABCG5/ABCG8.[146] Some parts of bile salts are secreted from hepatocytes into the portal vein through multidrug resistance-associated proteins (MRPs). In the presence of dietary fat, bile salts are delivered to the duodenum and enter the intestine, where they facilitate fat absorption.[147] After that, 95% of bile acids return to the liver by the process of enterohepatic circulation.[148] Na^+-taurocholate cotransporting polypeptide (NTCP/SLC10A1) and organic anion transporting polypeptides (OATPs/SLCOs) are responsible for sinusoidal bile acid reuptake into the hepatocytes.[148] PPARα seems to function as a critical regulator for all these processes. For example, PPARα activation upregulates the expression of genes encoding MRP3, MRP4, ABCB4, and ABCG5/ABCG8,[114,149] while *Ppara*-null mice have substantially decreased hepatic levels of mRNAs encoding transporters ABCB11, ABCB4, ABCG5, and ABCG8 and consequently resulted in the accumulation of bile acids in the liver during cholic acid challenge.[130] Treatment with PPARα agonist leads to a significant decrease of hepatic NTCP and OATP1 in mice, and these effects are abolished in *Ppara*-null mice,[114] suggesting PPARα-dependent suppression of bile acid reuptake into the hepatocytes. Moreover, human hydroxysteroid sulfotransferase 2A1 (SULT2A1)[122] and several UDP-glucuronosyltransferases (UGTs)[127–129,150] were identified as encoded by PPARα target genes. Increased levels of UGTs as a result of fibrate treatment were reported to promote bile acid glucuronidation, thereby reducing bile acid toxicity and increasing their

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urinary elimination.[121] Similarly, upregulation of SULT2A1 promoted bile acid sulfation and protected against bile acid-induced liver damage.[123]

Collectively, PPARα plays a critical role in reducing cholestatic hepatocellular injury. As a target gene of FXR, PPARα contributes to the negative feedback regulation of bile acid synthesis by inhibiting the expression of the rate-limiting enzyme CYP7A1. In addition, activation of PPARα promotes hepatic bile acid efflux and prevents their reuptake into the liver. Some PPARα target genes mediate the detoxification and metabolism of bile acids. Therefore, PPARα activation holds the potential to prevent cholestasis and cholestatic liver fibrosis.

PPARα TRANSREPRESSES INFLAMMATION

Inflammation is a protective response to infection, cellular stress, and injury,[151] and chronic inflammation is a driver of almost all major human diseases.[152] Undoubtedly, sustained exposure to hepatocellular injury and/or toxic agents contributing to the injury may disrupt liver homeostasis and lead to chronic inflammation that has become a common trigger for the development of fibrosis and cirrhosis.[1,28] Since an early finding revealed that *Pparα*-null mice have an enhanced inflammation response,[153] the crosstalk between PPARα and inflammation has been intensively studied.[27]

The mechanisms by which PPARα interacts with inflammation are complex (Box 4). On one hand, specific inflammatory signals reduce PPARα expression (Figure 3). Consistent with the downregulation of PPARα in patients with NASH[92] or virus hepatitis,[31] proinflammatory cytokines suppress the expression and activity of PPARα. For example, IL-1β was found to decrease PPARα signaling in mice and primary hepatocytes through repression of the *Pparα* promoter activity through the activation of NF-κB (Figure 3).[154] TNFα could lower *Pparα* mRNA expression by augmenting the activity of the canonical NF-κB signaling pathway in hepatocytes.[155] In contrast, the pharmacological IKK2 inhibitor AS602868 blocked liver fibrosis and steatohepatitis but activated PPARα and enhanced fatty acid oxidation.[157] These results revealed that NF-κB activation can directly modulate PPARα expression and activity, which orchestrates proinflammatory cytokine-induced interference of PPARα function. This is consistent with the hypothesis that there is a balance between PPARα-mediated anti-inflammatory activity and NF-κB-mediated proinflammatory signaling, and that the activation of NF-κB overwhelms PPARα, which may contribute to increased hepatic inflammation and fibrosis.[166] In addition to NF-κB, cytokines can interfere with PPARα through other mechanisms. IL-6 was reported to decrease PPARα expression and inhibit its transcriptional activity in HepG2 cells through the activation of CCAAT/enhancer-binding protein isoforms (C/EBPs)[156] or signal transduction and activator of transcription isoforms (STATs) (Figure 3).[158] STAT5b downregulates PPARα transcription by up to 80% through inhibition of ligand-independent activation function region-1 (AF-1) transactivation domain.[167] Therefore, under conditions with increased proinflammatory pressure, the functions of PPARα may be suppressed. Given that PPARα is a master regulator of lipid metabolism,[25–27] these findings provide a rationale for explaining that inflammatory responses exacerbate fat accumulation and lipotoxicity.[154]

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On the other hand, PPARα can counteract inflammation from various phases. The inflammatory response has 3 phases: inflammatory inducers (virus, toxins, or tissue injury), inflammatory sensors (macrophages), and inflammatory mediators (cytokines or chemokines).[168] Although there is still insufficient evidence that PPARα can improve viral hepatitis, PPARα activation does contribute to the suppression of inflammatory inducers through different mechanisms (Figure 3). For instance, PPARα agonists facilitate the removal of the harmful metabolite acetaldehyde derived from ethanol via increased aldehyde dehydrogenase activity.[57,59] Activation of PPARα clears lipotoxic fatty acids and their derivatives by transcriptionally promoting the expression of genes involved in fatty acid catabolism.[25,26] Fibrates prevent bile acid-induced hepatotoxicity through modulation of bile acid synthesis, secretion, and reuptake.[14,114] PPARα can induce the expression of catalase[54,55] and SOD1[56] to attenuate ROS production and oxidative stress-induced liver damage.

Moreover, metabolic reprogramming induced by PPARα activation may be involved in the immune response of macrophage.[169] As an inflammatory sensor, macrophage exists in 2 distinct populations: $CD68^{+}MARCO^{+}$ resident liver macrophages (KC) and recruited $CD68^{+}MARCO^{-}$ monocyte-derived hepatic macrophages, and a scar-associated $TREM2^{+}$ $CD9^{+}$ subpopulation of the latter is proinflammatory and profibrogenic and expands in liver fibrosis.[170] Given that the inflammatory macrophage has an enhanced glycolytic metabolism, while the anti-inflammatory macrophage is more dependent on fatty acid oxidation,[169] the increase of fatty acid oxidation by PPARα activation may support anti-inflammatory responses in macrophages.

Finally, the well-known mechanism for the anti-inflammatory role of PPARα is transcriptional repression of proinflammatory mediators (Figure 3). The first clue uncovering a role for PPARα in inflammation came from the finding that PPARα activation acted as a negative feedback mechanism to suppress inflammation.[153] Since then, many studies aimed at revealing the molecular pathways underlying this finding have been performed and have uncovered that more than 39 genes encoding inflammatory mediators are target genes of PPARα.[160] Notably, the majority of these genes are transrepressed by PPARα,[160] except IL-1 receptor antagonist (IL-1ra) that exhibits anti-inflammatory activity and is a direct target gene of PPARα with a functional PPRE present in the promoter,[171] indicating that the anti-inflammatory effects of PPARα may primarily stem from a PPRE-independent mechanism. Indeed, a study with DNA-binding-deficient PPARα mutant ($PPAR\alpha_{DISS}$) mice found that although activated $PPAR\alpha_{DISS}$ did not regulate target genes related to fatty acid oxidation, it protected against diet-induced liver damage and blunted inflammatory response and liver fibrosis.[21] Intriguingly, while PPARα expression is lower in human immune cells than in hepatocytes, some anti-inflammatory hormones transcriptionally upregulated PPARα transcript levels in T and B lymphocytes.[172] Macrophage PPARα was found to be a mediator of the anti-inflammatory effects of PPARα agonists,[173] as macrophage-specific *Pparα*-null mice failed to downregulate the proinflammatory cytokines IL-15 and IL-18.[173] Since proinflammatory mediators are tightly regulated by transcription factors including NF-κB,[174] activator protein-1 (AP-1),[175] STAT,[176] C/EBPs,[177] and nuclear factor of activated T-cells,[178] the interaction of PPARα with these transcription factors may contribute to the mechanism of the

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PPRE-independent transrepression of inflammation (Figure 3). As expected, growing evidence revealed that PPARα negatively regulates the activity of these transcription factors through different mechanisms.[20] Fibrates were reported to inhibit inflammatory response through PPARα by interfering with NF-κB and AP-1 transactivation capacity involving direct protein-protein interaction with p65 and c-Jun.[164] Palmitoylethanolammide-induced inhibition of NF-κB and subsequent inflammatory effects were proven to be dependent on PPARα, but not PPARγ.[179] It was found that PPARα activation controlled expression of the inhibitory kappa B kinase alpha (IκBα) in human cells and mice[22,] and WY-14,643 enhanced the phosphorylation of IκBα,[180] which was accompanied by a decrease in NF-κB DNA-binding activity.[22] Accumulating evidence indicated that PPARα activation accounted for the decrease in the production of proinflammatory mediators in different cell types through repression of NF-κB.[181,182] In addition, PPARα activators suppressed lipopolysaccharide-stimulated STAT1 phosphorylation and nuclear factor-binding activity, as a result suppressing the release of proinflammatory mediators.[165] The transcriptional activity of STAT5 was negatively regulated by PPARα containing the ligand-independent AF-1 transactivation domain.[161] Fibrates decreased the expression of C/EBPβ.[162,163] In summary, although PPARα has the potential to transactivate anti-inflammatory cytokines, the primary mechanism for the suppression of inflammation by PPARα is transcriptional repression of proinflammatory mediators.

Taken together, there is a balance between PPARα and inflammation (Figure 3). Increased inflammatory mediators may suppress PPARα signaling through different inflammatory transcription factors that potentiate the inflammatory response. This vicious circle is fully manifested under PPARα-deficient conditions. However, many inflammatory mediators are targets of PPARα. Ligand-activated PPARα acts through a transcriptional repression mechanism to decrease the inflammatory response by antagonizing transcription factor-mediated inflammatory mediators, thereby providing a potential rationale for protection against inflammation-associated fibrosis.

PPARα INDIRECTLY SUPPRESSES HSC ACTIVATION

HSCs are nonparenchymal liver pericytes that represent about 10% of all resident liver cells.[183] In normal liver, HSCs exist in a quiescent phenotype and act as the primary depot for storage of vitamin A.[184] Following liver cell damage and immune cell infiltration, HSCs can transdifferentiate into fibrogenic, proliferative, inflammatory, and chemotactic myofibroblasts, which is known as “activation,” and thus functions as a central driver of liver fibrosis.[1] Activation of HSCs is complex and multiple pathways including TGFβ/SMAD, Notch, Wnt/β-catenin, Hedgehog, and Hippo signaling pathways can activate HSCs.[1] A variety of stimuli from metabolic reprogramming, endoplasmic reticulum stress, oxidative stress, or epigenetic modifications can promote HSC activation.[1,185] Extracellular signals from various cells including hepatocytes, liver sinusoidal endothelial cells, macrophage, natural killer cells, and B cells also contribute to HSC activation.[1]

PPARα plays an indirect role in HSC activation (Box 5). Since fatty acids in HSCs primarily serves as an important substrate for the esterification of retinol rather than for energy production,[185] it is generally accepted that HSCs do not express PPARα,[2] a

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master transcription factor of fatty acid oxidation in hepatocytes.[25,26] In this context, direct activation of PPARα in HSCs should not cause significant effects on HSC function. As expected, evidence for direct activation of HSCs by PPARα is very limited and contradictory. While the inhibition of PPARα and related pathways were reported to orchestrate antioxidant-induced maintenance of quiescent lipocyte phenotype of HSCs,[190,191] suppression of PPARα expression was also found to mediate the promoting role of miR-33a in HSC activation,[192] and inactivation of human HSCs by adiponectin depends on PPARα transcriptional activity.[193] In contrast to PPARα, there was compelling evidence that PPARγ expression and activation consistently contributed to the inactivation of HSCs,[194,195] while PPARγ phosphorylation or loss of PPARγ activates HSCs.[196] These lines of evidence reinforce the view that HSC activation requires loss of lipid droplets, while the recovery of retinoid droplets inhibits HSC activation.[197,198] The latter is facilitated by the activation of lipogenic transcription factors[199,200] and may be potentially antagonized by PPARα. However, lack of convincing evidence for direct HSC activation by PPARα does not imply that PPARα is not involved in the modulation of HSC activation in the liver. Studies from animals and humans consistently suggested that PPARα ligands inhibited myofibroblast transformation and collagen synthesis of HSCs through various pathways,[11,186,201] while these beneficial effects were abolished in *Ppara*-null mice.[186] Moreover, as mentioned above, PPARα effectively prevents liver damage and inflammation caused by various etiologies, which may indirectly suppress HSC activation.

Indeed, current evidence suggested that PPARα modulates HSC activation through regulation of numerous extracellular signals released from different impaired cells (Figure 4). For example, hepatocytes, a major cellular target of hepatic damage and lipid accumulation, are a rich source of extracellular signals for HSC activation. Stressed or dead hepatocytes can activate HSCs through the release of profibrogenic damage-associated molecular patterns[28] or osteopontin,[202] while PPARα is involved in the damage-associated molecular pattern recognition process[187] and fenofibrate reduced serum and tissue levels of osteopontin.[188] Inflammatory cells activate HSCs through the release of proinflammatory cytokines,[203] while hepatic macrophage-specific PPARα disruption prevented the cytokine release[173,] and the transrepressive activity of PPARα was a prerequisite for the suppression of HSC activation.[21] Endothelial cell–mediated growth factor activation, another marker of cellular injury, has the potential to activate HSCs, which is prevented by PPARα agonists.[204] In addition, ROS released from different cells are important mediators to promote HSC activation.[205,206] Genetic disruption of PPARα was found to exacerbate oxidative stress and HSC activation,[68,189] while PPARα ligands ameliorated these effects.[12,55] Collectively, although the direct effects of PPARα on HSC activation remain unclear, various extracellular signals modulated by PPARα have emerged as critical drivers of HSC activation.

PPARα MODULATORS IN PRECLINICAL STUDIES

Consistent with the profound role of PPARα in preventing liver injury, inflammation, and HSC activation, preclinical studies have found that activation of PPARα by positive modulators can effectively suppress liver fibrosis, while inhibition of PPARα signaling by negative modulators may deteriorate or trigger fibrosis (Table 1).

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The well-known positive modulators of PPARα are the fibrate class of hyperlipidemic drugs. Current evidence from preclinical studies suggests that PPARα agonists have a comprehensive protective effect on fibrosis (Table 1). For example, the potent experimental PPARα agonist WY14,643 reversed diet-induced or ethanol-induced fibrosis and steatohepatitis in mice[11,70] through enhancing catalase activity,[66,213] inhibiting insulin resistance,[214] ameliorating hepatic cell death,[215] decreasing inflammatory cytokine TNFα,[70] blocking the activation of HSCs and macrophages,[11,70] and suppressing hepatic expression of profibrogenic cytokines osteopontin, TGF-β1, and matrix metalloproteinases.[11,70] Fenofibrate, a clinically used hypolipidemic agent and PPARα agonist, reduced hepatic lipotoxicity,[208] cholestatic liver injury,[14] inflammation,[209] and oxidative stress,[55] and subsequently prevented liver fibrosis derived from different causes.[82,209–211,222] Other fibrates such as bezafibrate[207] also ameliorated fibrosis in different models by reducing the TGF-β-induced myofibroblast differentiation and collagen protein formation. These lines of evidence suggest that PPARα activation can indirectly reverse fibrosis by reducing pro-fibrotic stimuli and activating cells responsible for promoting hepatic fibrosis.

Conventional fibrates are weak PPARα agonists with limited efficacy due to dose-related adverse effects.[251–253] Therefore, several novel agonists were developed that display either more selectivity toward PPARα, or dual PPARα/γ agonist, PPARα/δ agonist, pan-PPARα/γ/δ agonist, and multiple agonist activity toward PPARs and other targets. Among them, pemafibrate, a highly selective PPARα modulator (SPPARMα),[252,254] was proven to decrease fatty liver, inflammation, and fibrogenesis in murine models receiving a high-fat diet,[212] which highlights PPARα as a pivotal pharmacological target for liver fibrosis (Table 1). Elafibranor (GFT505), a dual PPARα/δ agonist, demonstrated liver-protective effects on inflammation and fibrosis in different animal models of NASH and liver fibrosis,[216] and the protective effects were mediated by both PPARα-dependent and PPARα-independent mechanisms,[216] indicating that the effects of PPARα and PPARδ on fibrosis may be synergistic. ZLY16, another novel highly potent PPARα/δ agonist, also decreased liver injury biomarkers, hepatic steatosis, inflammation, ballooning, oxidative stress, and fibrosis, and these effects were more favorable than elafibranor.[217] Moreover, an MHY2013 derivative was also identified as a dual PPARα/δ agonist and displayed antifibrotic effects.[218] A series of novel triazolone derivatives that exhibited more potent and well-balanced PPARα/δ agonistic activity than elafibranor prevented inflammation and liver fibrosis in preclinical models[219] (Table 1). These consistent and comprehensive hepatoprotective effects of PPARα/δ dual agonists indicate that they are promising liver-target drugs for the treatment of fibrosis. Besides, 3 PPARα/γ dual agonists include chiglitazar,[220] aleglitazar,[221] and saroglitazar[222,223] alleviated liver fibrosis in animal models by improving insulin resistance and dyslipidemia, inhibiting the TGF-β/SMAD signaling pathway, or modulating inflammatory cytokines and adiponectin. Given that PPARγ activation can directly inactivate HSCs[194,195] and PPARα indirectly suppresses HSC activation by modulating various extracellular signals, the synergistic protective effects of PPARα and PPARγ on fibrosis are logical. Owing to the potential synergistic effects of different PPAR subtypes, antifibrotic effects of pan-agonists have also been explored. Notably, a pan-PPAR agonist lanifibranor (IVA337) combined the beneficial effects of selective PPAR agonists and displayed an antifibrotic efficacy superior to selective PPARα,

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PPARδ, or PPARγ agonists.[224,225] MBT1805, a pan-agonist with a balanced PPARα/γ/δ activation effect, relieved α-naphthylisothiocyanate-induced necrosis, vacuolation, and inflammatory infiltration by regulating bile acid synthesis, biotransformation, and transport.[226] Intriguingly, quadruple agonists have also been developed for the treatment of liver fibrosis (Table 1). One example is RLA8, a novel and balanced quadruple agonist for hepatic lipid metabolism and inflammation-related PPARα/γ/δ and G protein-coupled receptor 40 (GPR40). Results from 2 mouse NASH models (induced by a methionine/choline-deficient diet or by a high-fat diet) showed that RLA8 reversed NASH-induced liver damage such as steatosis, inflammation, and fibrosis by reducing lipotoxicity and oxidative stress through activating PPARs and GPR40.[227] Based on this agonist, a newly developed quadruple ZLY18 exhibited far stronger lipid-lowering effects and twice higher metabolic half-life than that of RLA8.[228] In the NASH model, ZLY18 reversed hyperlipidemia to an almost normal level, and significantly decreased hepatocellular ballooning, inflammation, and liver fibrosis even better than RLA8.[228] In addition, ZLY18 is more effective than PPARα agonists in the prevention of CCl_4-induced liver fibrosis.[228]

In addition to synthetic PPARα agonists, PPARα seems to mediate the beneficial effects of a series of chemicals or oligonucleotides on ameliorating fibrosis (Table 1). For example, the lipids oleoylethanolamide and palmitoylethanolamide are representative endogenous PPARα ligands. They both significantly reduced inflammatory cytokines, blocked HSC activation, and attenuated liver fibrosis in animal models, and these protective effects were abolished in *Ppara*-null mice.[186] It was reported that the mechanism of oleoylethanolamide in the inactivation of HSCs is mediated by suppressing SMAD2/3 phosphorylation, α-SMA expression, and myofibroblast transformation.[186] Similar to these ligands, there are a large number of natural or synthetic chemicals that are capable to counteract liver fibrosis and activate or upregulate PPARα, including pirfenidone,[229,230] melatonin,[75] ascorbic acid,[231] chicory seed extract,[232] epigallocatechin gallate,[107] syringic acid,[233] glycyrrhizic acid,[234] 2,3,5,4'-tetrahydroxystilbene-2-O-β-d-glucoside,[235] 4-O'-methylhonokiol,[78] iso-alpha acids,[236] baicalin,[237] betanin,[238] calycosin,[239] naringenin,[240] conophylline,[241] curcumin,[242] quercetin,[243] perfluorooctanoate,[244] alisol B 23-acetate, [245] and telmisartan.[246] Although evidence is still lacking to support whether the antifibrotic effects of these chemicals are PPARα-dependent, these consistent results suggest that PPARα may be a potential common mediator for their protective role in fibrosis. Moreover, some oligonucleotides were reported to prevent fibrosis through upregulating PPARα, such as periostin antisense oligonucleotide[247] and circRNA_0046367.[248]

In contrast, different microRNAs (miRs) that negatively modulate PPARα can trigger hepatic fibrosis (Table 1). A typical example is miR-21 that has been implicated in both hepatic and renal fibrosis.[249,255,256] PPARα is a known target of miR-21,[257] and miR-21 overexpression decreases PPARα levels and signaling, while miR-21 knockout increases PPARα expression and lipid metabolism.[256] Through activating the TGF-β1/SMAD3 pathway[255] or silencing lipid metabolic pathways,[256] miR-21 promoted fibrogenesis by suppressing PPARα. Inhibition of miR-21 expression, on the contrary, restored PPARα expression and reduced liver cell injury, inflammation, and fibrogenesis, while these effects were lost in *Ppara*-null mice,[249] suggesting the PPARα-dependent profibrogenic role

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of miR-21. Moreover, caloric restriction[258] and quercetin[243] were found to alleviate fibrosis through suppression of miR-21 and upregulation of PPARα. Therefore, miR-21 may involve in the development of fibrosis by targeting PPARα. Similar to miR-21, other proinflammatory and profibrogenic miRs were also discovered to decrease PPARα, such as miR-27,[33] miR-33a,[192] miR-155,[65] and miR-540.[250]

Collectively, these data reinforce the view that PPARα is a potential therapeutic target for hepatic fibrosis. The discovery of abundant novel agonists, natural chemicals, or oligonucleotides has led to the expectation of effective antifibrotic drugs by targeting PPARα.

PPARα-RELATED AGENTS IN CLINICAL TRIALS

Although liver fibrosis is a serious health problem worldwide and can easily lead to cirrhosis and liver failure, there is no effective strategy available for the treatment except removal of the causative agents or liver transplantation.[5] Substantial progress in preclinical studies targeting PPARα has thrown new light on the development of antifibrotic drugs. Currently, several clinical studies related to PPARα have shown promise and are undergoing further evaluation (Table 2).

Given the robust preclinical data, fibrates remain active molecules in the development of antifibrotic drugs through targeting PPARα. As a class of clinically used hypolipidemic drugs since the 1930s, fibrates function to facilitate lipid metabolism and decrease bile acid synthesis. Therefore, it is presumed that fibrates may prevent lipotoxicity and harmful levels of bile acids and may improve liver fibrosis in patients with NAFLD and cholestasis. To develop antifibrotic drugs, 3 fibrates are undergoing assessment in clinical trials (Table 2), including fenofibrate (NCT02891408 in phase 1, NCT02781584, NCT02354976, and NCT00575042 in phase 2), pemafibrate (NCT03350165 in phase 2), and bezafibrate (NCT01654731, NCT02701166, and NCT02937012 in phase 3). In NAFLD patients, fenofibrate (145 mg/d or 200 mg/d) treated for 2 or 12 weeks only effectively mitigated hypertriglyceridemia but not fibrosis,[263,264] while pemafibrate (K-877) treatment significantly improved dyslipidemia[278,279] and reduced magnetic resonance elastography–based liver stiffness,[266] a noninvasive measure of liver fibrosis. Since pemafibrate is one of the novel SPPARMαs that has superior balance of efficacy and safety compared with conventional fibrates,[252] the benefits of pemafibrate on fibrosis indicate that PPARα is a therapeutic target for liver fibrosis, and new SPPARMα may potentially be useful clinically. In patients with PBC and primary sclerosing cholangitis, short-term (21 d) bezafibrate treatment effectively attenuated moderate to severe pruritus.[260] Among patients with PBC who had an inadequate response to ursodeoxycholic acid (UDCA) alone, treatment with bezafibrate in addition to UDCA for 3 months significantly reduced bile acid synthesis and improved serum biliary enzymes, Ig M, cholesterol, and triglyceride concentrations,[261,262] and for 24 months improved biochemical response, pruritus, fatigue, and noninvasive measures of liver fibrosis, including liver stiffness and enhanced liver fibrosis score.[259] Consistently, combination therapy with fenofibrate and UDCA for 48 weeks in PBC patients significantly improved fibrosis as indicated by lower serum alkaline phosphatase (ALP)

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activity.[265] Collectively, these data from clinical trials suggest that fibrates are potential therapeutic agents for liver fibrosis, especially cholestatic liver fibrosis.

Intriguingly, fibroblast growth factor 21 (FGF21), a protein encoded by the PPARα target gene *FGF21*, was recently found to be anti-fibrotic and can cause considerable pharmacological benefits on a cluster of metabolic diseases.[280] Several FGF21 mimetics have progressed to early phases of clinical trials (Table 2), such as pegbelfermin (NCT03445208 and NCT03674476 in phase 1, and NCT02413372, NCT03400163, NCT03486899, and NCT03486912 in phase 2) and efruxifermin (NCT03976401 in phase 2). In a phase 2a study in patients with biopsy-confirmed NASH and stage 1–3 fibrosis, treatment with subcutaneously administered pegbelfermin (BMS-986036) for 16 weeks significantly reduced hepatic fat content and liver transaminases, increased serum levels of adiponectin, improved lipid profiles, and attenuated hepatic injury and biomarkers of fibrosis.[268] To expand on the phase 2a results, 2 phase 2b randomized, double-blinded, placebo-controlled studies were designed to assess the efficacy and safety of pegbelfermin in the treatment of patients with NASH and bridging fibrosis or compensated cirrhosis.[269] In another phase 2a study in patients with NASH and fibrosis, administration of efruxifermin through weekly subcutaneous injection for 16 weeks was proven to be safe and efficacious in reducing hepatic fat and markers of liver injury and fibrosis.[270] These data indicate that specific PPARα modulators may improve liver fibrosis through upregulating FGF21.

Based on the hypothesis that agonists with dual or multiple targets will combine the advantages and minimize the side effects caused by selective agonists, the development of modulators with dual or multiple agonist activity toward PPARs and other targets has become a promising strategy for designing effective agents against liver fibrosis. Not surprisingly, given the abundance of preclinical data from mice, several agonists with dual or pan-agonism to PPARs have been tested in phase 2 or phase 3 clinical trials for liver fibrosis (Table 2), including elafibranor (NCT03124108, NCT04526665, NCT01694849, and NCT02704403), saroglitazar (NCT03061721, NCT03112681, and NCT03863574), and lanifibranor (NCT03008070, NCT03459079, and NCT04849728). Although direct evidence for most of these agonists in the regression of liver fibrosis is still being evaluated, current results from clinical trials suggest that they may improve fibrosis through the resolution of causative etiologies or prevention against liver injury.

As a dual PPARα/δ agonist, elafibranor (GFT505) was reported to improve lipid metabolism, insulin resistance, inflammation, and fibrosis in preclinical studies.[281,282] Consistent with these results, in abdominally obese patients, elafibranor significantly reduced fasting plasma triglycerides and enhanced insulin sensitivity.[283,284] Intriguingly, this agonist seems to act in a liver-dependent manner, as it fails to induce PPARα or PPARδ target genes in the skeletal muscle.[283] In the GOLDEN study that is a phase 2 multicenter, double-blinded, randomized controlled trial in 91 adult patients with noncirrhotic NASH, elafibranor (120 mg/d for 1 y) resolved NASH without worsening of fibrosis.[272] Moreover, those patients who achieved resolution of NASH after receiving elafibranor also showed strong reductions in fibrosis, hepatocyte ballooning, lobular steatosis, and the NAFLD activity score (NAS), as well as systemic inflammatory markers such as C-reactive protein, fibrinogen, and haptoglobin.[272] However, in the RESOLVE-IT study which is a phase

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3 trial (NCT02704403) in 2000 NASH patients with stage 2–3 fibrosis, elafibranor (120 mg/day for 72 wk) did not show any statistically significant effect on the predefined primary endpoint of NASH resolution without worsening of fibrosis, and therefore, the trial was discontinued. Notably, the reason why elafibranor failed to resolve NASH in this study remains unclear, and it cannot be ruled out that more advanced fibrosis is less "regressible." In a double-blinded, randomized placebo-controlled phase 2 trial in 45 patients with PBC and incomplete response to UDCA, elafibranor (80 mg/d or 120 mg/d for 12 wk) successfully decreased levels of disease markers, including fibrosis marker serum ALP.[271] Taken together, although the treatment of liver fibrosis with elafibranor has met with a disappointing failure in phase 3 trial in NASH patients, the clinical study of elafibranor in PBC patients has shown promise.

Saroglitazar (ZYH1), a dual PPARα/γ agonist, was shown to improve hepatocyte steatosis, insulin resistance, and inflammation, and prevent the development of fibrosis in animal studies.[77,223,285] In a proof-of-concept study that is a double-blinded phase 2 proof-of-concept trial in 37 patients with PBC and UDCA resistant or intolerant, saroglitazar (2 mg/d or 4 mg/d for 16 wk) led to a rapid and sustained improvement in ALP.[274,275] In a multicenter, prospective, randomized, double-blinded, placebo-controlled proof-of-concept study in 16 adult patients with NASH, treatment with saroglitazar (4 mg and 2 mg for 24 wk) resulted in resolution of steatohepatitis with no worsening of fibrosis[13] and marked improvement in hepatocyte ballooning and steatosis, as well as reduction in serum levels of triglycerides and total cholesterol.[13] In a randomized, controlled, double-blinded phase 2 trial in 106 patients with NAFLD/NASH, saroglitazar at 1, 2, or 4 mg for 16 weeks reduced serum ALT levels by 25.5%, 27.7%, and 45.8%, respectively,[273] and saroglitazar 4 mg also significantly improved liver fat content, fibrosis, insulin resistance, and atherogenic dyslipidemia.[273] Taken together, current evidence from clinical studies suggests that saroglitazar is effective in improvement of liver injury and fibrosis in both patients with PBC or NASH. These findings support further assessment of saroglitazar in phase 3 trials.

Lanifibranor (IVA337) is a moderately potent and well-balanced pan-PPAR agonist, [(106) which] demonstrated excellent antihyperglycemic and hypolipidemic efficacy and anti-fibrotic activity in animal models.[106,286] To assess the therapeutic potential of IVA337, the efficacy and the safety of 2 doses of IVA337 (800 mg, 1200 mg) per day for 24 weeks were evaluated in the NATIVE study which is a phase 2b, double-blinded, randomized, placebo-controlled trial in 247 adult patients with noncirrhotic NASH.[276,277] The results revealed that IVA337 resolved NASH and improved fibrosis according to histological evaluations by biopsy.[277] Based on these findings, a phase 3 study (NCT04849728) is being conducted to evaluate long-term efficacy and safety of lanifibranor in adult NASH patients with stage 2–3 fibrosis.

Collectively, current clinical trials suggest that novel SPPARMα and some agonists with dual or multiple targets including PPARα hold promise for antifibrotic drugs. These data indicate that the development of novel compounds with more selectivity to PPARα or with synergetic agonism to PPARα and other fibrotic molecular targets will be potentially effective strategies for the development of antifibrotic drugs. While the long-term efficacy and safety of these agonists are still under evaluation, these favorable results open a window

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for the development of effective antifibrotic drugs through targeting PPARα and related molecules.

CHALLENGES AND UNMET NEEDS

Although a great number of PPARα modulators have shown promise in preventing or regressing liver fibrosis in experimental models, there are some challenges and unmet needs that hamper the translation of mouse data into human liver disease treatments (Box 6).

A. Species differences: in rodents, exposure to PPARα agonists has been associated with peroxisome proliferation, hepatomegaly, and liver cancer, which have not been observed in humans. The reason for this species difference may be attributable to truncated human PPARα splice variants[287] and human PPARα mRNA expression at one-tenth the level of mouse.[288] To address these challenges, a *PPARA*-humanized mouse strain was created. Current evidence shows that agonist-induced hepatomegaly and hepatocarcinogenesis are abolished in *PPARA*-humanized mice,[289] suggesting that this mouse strain is a valuable tool for examining species-specific responses to PPARα agonists. However, the application of this strain in fibrosis regression studies is still very limited.

B. Safety of PPARα agonists: the long-term use of conventional fibrates was reported to increase the risk of cholesterol gallstone and other dose-dependent adverse events in patients.[251–253] Although novel compounds with PPARα agonism display higher efficacy and safety than conventional fibrates, the long-term safety of these compounds remains to be further evaluated.

C. Complex molecular mechanisms of liver fibrosis: liver fibrosis is increasingly considered as a highly complex disorder with multiple molecular mechanisms driving disease progression. Currently, in addition to PPARα, many other fibrotic molecular targets have been identified,[1] which means that drugs targeting a variety of orthogonal mechanisms may be more effective in resolving liver fibrosis than those targeting a single mechanism. Consistent with this concept, novel compounds with synergistic agonism to PPARα and one or more other molecular targets have been designed, some of which have shown higher antifibrotic efficacy than PPARα-selective agonists in both animal and clinical studies. However, there are still no trials testing the efficacy of drug cocktails targeting several mechanisms in treating liver fibrosis.

D. Broad functions of PPARα: PPARα regulates extensive physiological functions through modulating the expression of a considerable number of target genes, while not all these targets contribute to the prevention of hepatic fibrosis. The successful suppression of fibrosis by FGF21 mimics in clinical trials[268,270] and selective modulation of PPARα transrepression activity in a preclinical study[21] suggest that it should be a promising strategy for the development of effective antifibrotic drugs through the creation of novel ligands with selective activity for specific PPARα functions. However, such PPARα agonists have not been designed, and the functional selectivity of available agonists remains

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to be explored. In addition, NASH in humans and mice was associated with the increase of intestinal PPARα and its target gene *Fabp1* encoding fatty acid-binding protein (FABP1), while genetic ablation of PPARα or FABP1 specifically in intestine epithelial cells abolished NASH in mice fed a high-fat, high-cholesterol, and high-fructose diet,[290] which suggests that PPARα in different organs plays different roles in the development of fibrosis. Although hepatic PPARα was reported to mediate the major metabolic effects of Wy-14,643,[291] the organ-specific role of most PPARα agonists remains unclear.

E. Variable composition of myofibroblasts: Since activated HSCs are believed to be the primary source of fibrogenic myofibroblasts in the liver,[7] the cellular mechanisms of liver fibrosis is predominantly HSC centric.[5] Available evidence suggests that the composition of myofibroblasts may vary substantially across etiologies of hepatic fibrosis.[1] However, HSCs do not seem to express PPARα. Although the indirect inhibitory role of PPARα agonists in HSC activation has been intensively studied, the potential role of PPARα in other sources of hepatic myofibroblasts remains to be explored.

F. Multiple principles of antifibrotic therapy: Several PPARα agonists have shown significant antifibrotic activity in both animal and clinical studies, but the principles underlying different antifibrotic therapies should not be identical. In patients or animal models with mild to moderate fibrosis, the beneficial role of PPARα agonists may stem from attenuating disease progression, whereas in those with advanced fibrosis, their antifibrotic effects may be associated with enhanced matrix degradation. However, while PPARα activation plays protective roles in fibrogenesis through suppression of hepatocellular injury, inflammation, and HSC activation, there is no direct evidence that PPARα agonists can induce matrix degradation.

G. Etiology-specific effects of PPARα: It is generally believed that the pathogenesis of liver fibrosis varies according to the etiology, which may explain why some PPARα agonists can only improve fibrosis in specific experimental models or patients. In fact, the expression and activity of PPARα are affected by various pathophysiological conditions including disease, stress, hormones, cytokines, and kinases,[27] and these factors may also impact the effects of PPARα modulators on hepatic fibrosis. Hence, it is important to test the efficacy of these modulators in patients with fibrosis derived from different etiologies. However, the etiology-specific effects of different agonists remain to be elucidated.

H. Insensitive trial endpoints: Recently, the discovery of powerful biomarkers and the successful development of molecular imaging of fibrosis have enabled noninvasive, rapid, and longitudinal readouts of drug efficacy in antifibrotic trials. However, endpoints in current clinical studies evaluating the anti-fibrotic effects of PPARα agonists do not incorporate these noninvasive measures, but instead mainly assess liver histology or serum ALP. Therefore, data on the dynamics of gradual improvement in fibrosis induced by PPARα agonists in patients are still lacking.

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SUMMARY AND PROSPECTS

Hepatic fibrosis, which arises from a persistent wound-healing response to liver injury, has become a global health problem as it can easily develop into cirrhosis, HCC, and liver failure. However, antifibrotic drug development remains limited. Uncovering the pathophysiological mechanisms of hepatic fibrosis would provide potential therapeutic targets for the development of effective antifibrotic drugs. After 4 decades of steady progress, it is clear now that the pathogenesis of hepatic fibrosis is initiated by liver injury derived from different etiologies, and liver injury triggered inflammation and subsequent HSC activation through various signaling pathways accounting for fibrogenesis.[1] Therefore, a molecular target that could defend against or inhibit all these processes is urgently needed.

PPARα is a ligand-inducible transcriptional modulator of key metabolic processes, as well as inflammation, oxidative stress, and HSC activation. Therefore, PPARα might be a promising therapeutic target for hepatic fibrosis. Dysregulation or suppression of PPARα is a common feature in most causative etiologies of hepatic fibrosis,[31,61,65,92] and PPARα deficiency predisposes animals to hepatic fibrosis in different disease models. In contrast, hepatic PPARα activation seems to act as a modulator of hepatic fibrosis originating from different causative agents by preventing liver injury and subsequent inflammation and HSC activation. As a master regulator of lipid metabolism, PPARα governs the clearance of harmful lipids and the prevention of lipotoxicity. Through transcriptional modulation of bile acid synthesis and drug metabolism, PPARα expression and activity contribute to the detoxification of toxic bile acids and chemicals. The transrepressive activity of PPARα on inflammation is necessary and sufficient to prevent liver fibrosis. Moreover, preclinical studies have revealed a plethora of PPARα modulators, including chemicals or oligonucleotides, that have the potential to impact the development of hepatic fibrosis, which will serve as a resource for the development of antifibrotic drugs.

Collectively, PPARα is a potential therapeutic target for hepatic fibrosis. The development of compounds with selective activity for PPARα or synergetic agonism to PPARα and other targets holds promise to develop effective antifibrotic drugs. These translational approaches are enabling the emergence of precision medicine-based therapies for patients with hepatic fibrosis.

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Abbreviations:

ABCs	ATP-binding cassette transport proteins
ACADM	acyl-CoA dehydrogenase medium chain

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ACOX	acyl-CoA oxidase 1
ADH	alcohol dehydrogenase
AF-1	activation function region-1
ALD	alcoholic liver disease
ALDH	aldehyde dehydrogenase
ALP	alkaline phosphatase
AP-1	activator protein-1
CA	cholic acid
CAT	catalase
CCl4	carbon tetrachloride
CDCA	chenodeoxycholic acid
C/EBP	CCAAT/enhancer-binding protein isoform
CYP	cytochromes P450
DAMP	damage-associated molecular pattern
DBD	DNA binding domain
ECM	extracellular matrix
FABP1	fatty acid binding protein
FFA	free fatty acid
GF21	fibroblast growth factor 21
FXR	farnesoid X receptor
GPR40	G protein-coupled receptor 40
HBV	hepatitis B virus
HCV	hepatitis C virus
HNF4α	hepa tocyte nuclea r fa ctor 4α
HSC	hepatic stellate cell
IκBα	inhibitory kappa B kinase alpha
IL-1β	interleukin-1β
IL-1ra	interleukin-1 receptor antagonist
LBD	ligand binding domain

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miR	microRNA
MRE	magnetic resonance elastography
MRP	multidrug resistance-associated proteins
NAD+	nicotinamide adenine dinucleotide
NADH	reduced form of nicotinamide-adenine dinucleotide
NAFLD	nonalcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NFAT	nuclear factor of activated T-cells
NF-κB	nuclear factor kappa B
NTCP//SLC10A1	Na+-taurocholate cotransporting polypeptide
OATPs/SLCOs	organic anion transporting polypeptides
PBC	primary biliary cirrhosis
PPARα	peroxisome proliferator-activated receptor alpha
PPARδ	peroxisome proliferator-activated receptor delta
PPARγ	peroxisome proliferator-activated receptor gamma
PPRE	peroxisome proliferators response element
PSC	primary sclerosing cholangitis
ROS	reactive oxygen species
RXR	retinoid X receptor
SHP	small heterodimer partner
α-SMA	alpha smooth muscle actin
SOD1	CuZn-superoxide dismutase
SPPARMα	selective PPARα modula tor
STAT	signal transduction and activator of transcription isoform
SULT2A1	sulfotransferase 2A1
TGF-β1	transforming growth factor-beta 1
TNFα	tumor necrosis factor alpha
XAP2	X-associated protein 2
UGTs	UDP-glucuronosyltransferases

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Box 1

Key points for PPARα and ethanol-related hepatotoxicity

Ethanol metabolism inactivates PPARα

- Acetaldehyde directly inhibits PPARα transcription and activity.[60,61]
- ROS suppresses PPARα activity using adiponectin.[62]
- Adenosine suppresses PPARα activity using zinc.[63,64]
- Ethanol upregulates miR-155 prevents PPARα translation.[65]

PPARα activation detoxifies ethanol-related hepatotoxicity

- PPARα activation promotes fatty acid catabolism.[25,26]
- PPARα activation increases the expression of catalase[54,55] and SOD1.[56]
- PPARα activation facilitates acetaldehyde removal.[57,59]
- PPARα activation accelerates ethanol clearance via the catalase pathway.[66]

Evidence for PPARα involvement in ethanol-induced hepatotoxicity

- PPARα deficiency exacerbates ethanol-induced liver injury and steatosis.[67,68]
- Suppression of miR-155 abrogates ethanol-induced liver lesions.[65]
- A decrease in PPARα signaling promotes ethanol-induced liver injury.[69]
- PPARα agonists prevent ethanol-arisen liver injury.[68–70]

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Box 2

Key points for PPARα involvement in NAFLD

- NAFLD severity is negatively correlated with hepatic PPARα expression.[92]
- Fatty acids are endogenous PPARα ligands.[93]
- PPARα governs most lipid metabolic processes.[26]
- PPARα activation promotes the clearance of lipotoxic fatty acids.[25–27]
- PPARα deficiency increases fat accumulation and lipotoxicity.[94–96]

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Box 3

Key points for PPARα preventing bile acid-induced hepatotoxicity

PPARα activation reduces bile acid accumulation in hepatocytes

- PPARα agonists reduce serum bile acid concentrations.[116,117]
- PPARα activation decreases de novo synthesis of bile acid.[118]
- *Ppara*-null mice have increased serum total bile acids.[119]
- PPARα activation suppresses bile acid reuptake and reabsorption.[114]

PPARα activation detoxifies bile acids

- PPARα activation increases biliary phosphatidylcholine secretion.[120]
- PPARα activation enhances bile acid glucuronidation and urinary elimination.[121]
- PPARα activation enhances bile acid metabolism and detoxification.[122,123]

PPARα activation prevents bile acid-induced oxidative stress

- PPARα activation attenuates cholestatic oxidative stress.[124]

Evidence for PPARα involvement in bile acid homeostasis

- Bile acids upregulate PPARα gene expression by activating FXR.[113]
- Several PPARα target genes contribute to bile acid homeostasis.[120,122,125–129]
- Bile acid homeostasis was disrupted in cholic acid treated *Ppara*-null mice.[130]

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Box 4

Key points for the interaction of PPARα with inflammation

Proinflammatory signaling suppresses PPARα expression and activity

- IL-1β, IL-6, and TNFα decrease PPARα expression.[154–156]
- NF-κB, C/EBPs, and STAT5b represses PPARα expression and activity.[156–158]

PPARα activation suppresses inflammation

- PPARα activation promotes the clearance of inflammatory mediators.[25,26,54–57,59]
- PPARα activation contributes to anti-inflammatory responses in macrophages.[159]
- PPARα activation downregulates inflammatory cytokines.[160]
- PPARα activation represses inflammatory transcription factors NF-κB, AP-1, STAT, C/EBPs, and NFAT.[161–165]
- Pharmacologically activated PPARα inhibited hepatic inflammatory responses.[21]
- *Ppara*-null enhances inflammatory response.[153]

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Box 5

Key points for PPARα in the regulation of HSC activation

Pharmacologically activated PPARα inhibits HSC activation

- Wy-14,643 prevents HSC activation.[11,173]
- Oleoylethanolamide blocks HSC activation.[186]
- Loss of PPARα abolishes agonist-induced suppression of HSC activation.[173,186]

PPARα activation suppresses stimuli for HSC activation

- PPARα agonists promote the release of anti-inflammatory cytokines.[173]
- PPARα activation decreases lipid peroxidation.[11]
- PPARα activation reduces ROS levels.[12,55]
- PPARα activation represses the release of profibrogenic mediators.[187,188]
- PPARα deficiency exacerbates oxidative stress and inflammation.[21,68,189]

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Box 6

Key points for challenges and unmet needs

- Species differences between mouse and human PPARα in responses to agonists.
- Unclear long-term safety profiles of PPARα agonists.
- Lack of synergistic therapeutic strategies against multiple targets in liver fibrosis.
- Undefined functional selectivity and organ-specificity of PPARα agonists.
- Unknown roles of PPARα in non–HSC-derived myofibroblasts.
- Uncertain principles of PPARα agonists in antifibrotic therapy.
- Absence of etiology-specific effect of PPARα agonists on liver fibrosis.
- Outdated endpoints in PPARα agonist trials.

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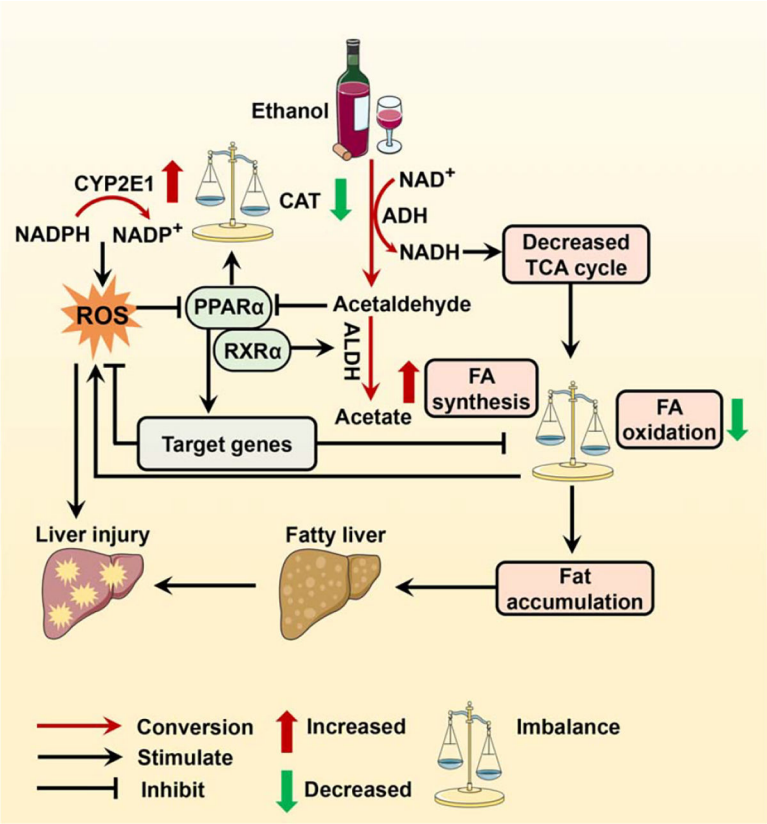

FIGURE 1.

Role of PPARα in alcohol metabolism. Ethanol is metabolized by ADH, CYP2E1, and CAT to produce acetaldehyde. Toxic acetaldehyde and CYP2E1-generated ROS can induce hepatocellular injury by inactivating PPARα. PPARα activation enhances detoxification of FFA-derived lipotoxicity by modulating the expression of most key genes involved in FA catabolism and suppresses ROS production by switching alcohol metabolism from the CYP2E1 pathway to the CAT pathway, which restores the balance between oxidants and antioxidants, FA oxidation and synthesis, and thus prevents alcohol-arisen liver injury. Abbreviations: ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; CAT, catalase; CYP2E1, cytochrome P450 2E1; FA, fatty acid; FFA, free fatty acid; PPARα, peroxisome proliferator-activated receptor alpha; ROS, reactive oxygen species; RXRα, retinoid X receptor.

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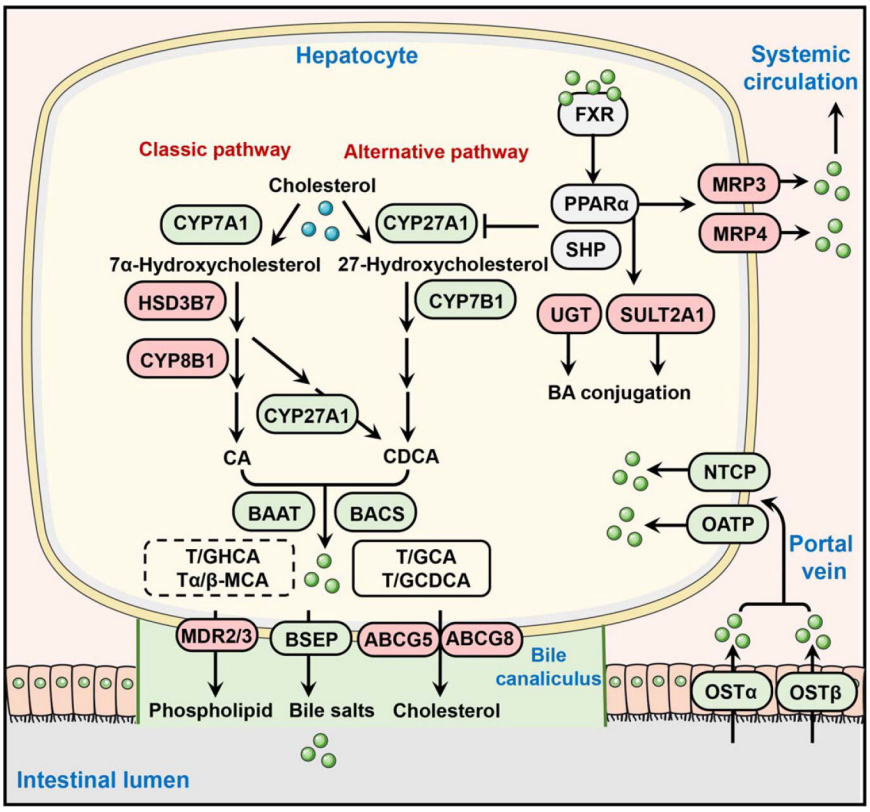

FIGURE 2.

Role of PPARα in the regulation of bile acid synthesis, transport, and metabolism. Bile acids activate the FXR-PPARα axis in hepatocytes to suppress bile acid synthesis primarily by inhibiting CYP7A1 (classic pathway) and CYP27A1 (alternative pathway). The activation of PPARα also promotes bile acid efflux from hepatocytes into the portal vein by induction of MRP3 and MRP4, and into bile canaliculus by induction of MDR2/MDR3 and ABCG5/ABCG8. In addition, PPARα activation represses bile acid reuptake into the liver by downregulating bile acid transporter OATP, NTCP, and OSTβ, as well as enhances the detoxification and metabolism of bile acids through the regulation of some target genes such as UGTs and SULT2A1. PPARα activation upregulates proteins. Filled green circles represent bile acids. Proteins upregulated by PPARα are shaded in red, and those downregulated by PPARα in green. Abbreviations: ABCG, ATP-binding cassette subfamily G; BAAT, bile acid-CoA: amino acid N-acyltransferase; BACS, bile acid-CoA synthetase; BSEP, bile salt export pump; CA, cholic acid; CDCA, chenodeoxycholic acid; CYP7A1, cytochrome P450 7A1; CYP7B1, cytochrome P450 7B1; CYP8B1, cytochrome P450 8B1; CYP27A1, cytochrome P450 27A1; FXR, farnesoid X receptor; HSD3B7, 3 beta-hydroxysteroid dehydrogenase type 7; MDR2/3, multidrug resistance protein 2/3; MRP, multidrug resistance-associated protein; NTCP, sodium/taurocholate cotransporting polypeptide; OATP, organic anion-transporting polypeptide; OSTα/β, organic solute transporter subunit α/β; PPARα, peroxisome proliferator-activated receptor alpha; SULT2A1, sulfotransferase 2A1; UGT, UDP-glucuronosyltransferase.

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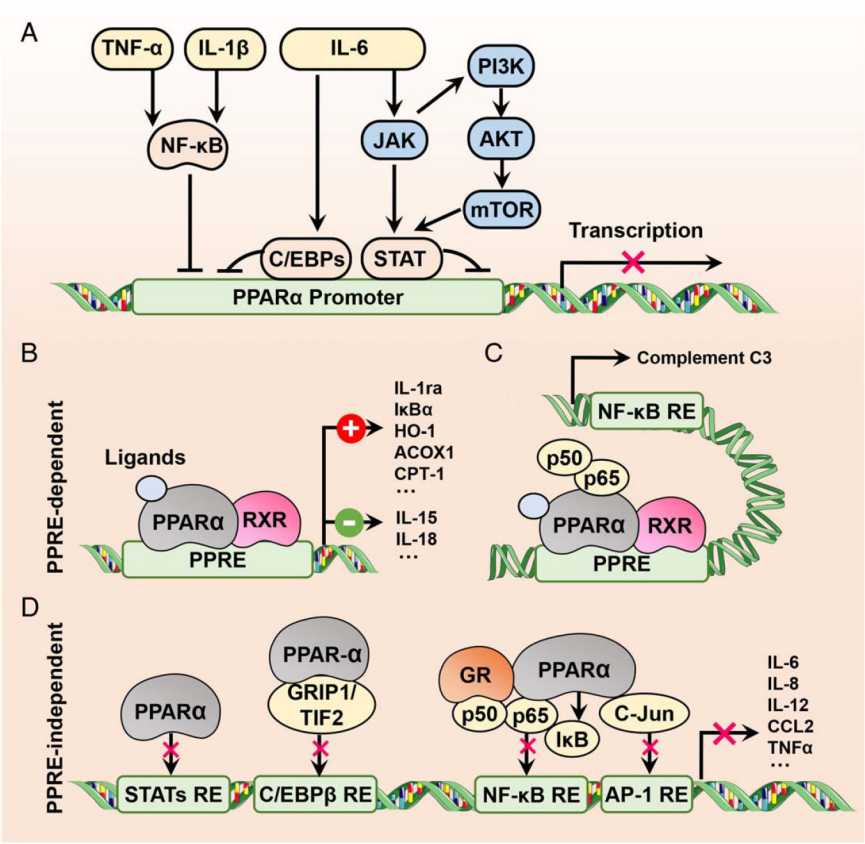

FIGURE 3.

Crosstalk between PPARα and inflammation. (A) Inflammatory cytokine-induced suppression of PPARα activity and/or expression using different proinflammatory transcription factors such as NF-κB, C/EBPs, and STATs. (B) PPARα activation-induced protection against inflammation through downregulating (−) proinflammatory cytokines or upregulating (+) anti-inflammatory factors in a PPRE-dependent manner. (C) Inhibition of NF-κB transcriptional activity by activated PPARα through PPRE-dependent abrogation of p65 binding to an NF-κB response element in the complement C3 promoter. (D) PPRE-independent inhibition of transrepression of proinflammatory cytokines. The transcriptional activity of proinflammatory transcription factors can be directly inhibited by PPARα or indirectly blocked by the interaction of PPARα with proteins. Abbreviations: ACOX1, acyl-CoA oxidase 1; AP-1, activator protein-1; C/EBPs, CCAAT/enhancer-binding protein isoforms; CCL2, C-C motif chemokine ligand 2; CPT-1, carnitine palmitoyltransferase-1; GR, glucocorticoid receptor; GRIP1, glucocorticoid receptor-interacting protein 1; HO-1, heme oxygenase-1; IL-1ra, IL-1 receptor antagonist; IκBα, inhibitor of NF-κB alpha; PPARα, peroxisome proliferator-activated receptor alpha; PPRE, PPAR-response element; RXR, retinoid X receptor; STATs, signal transduction and activator of transcription isoforms; TIF2, transcriptional intermediary factor 2.

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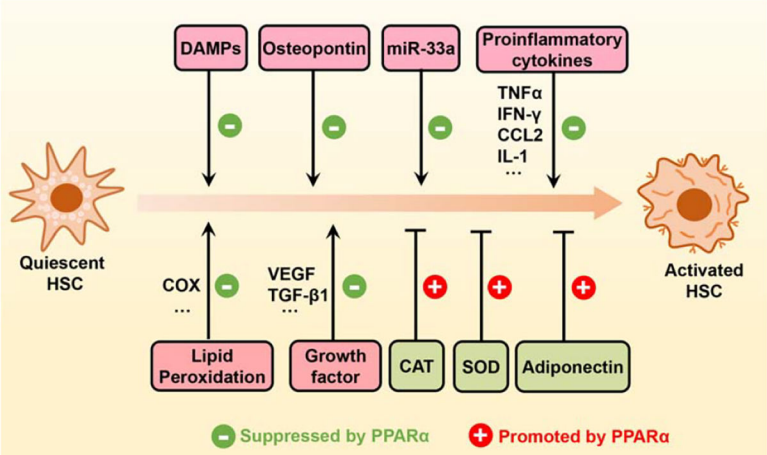

FIGURE 4.

PPARα activation indirectly suppresses HSC activation. Upon ligand activation, PPARα can inhibit HSC activation through different mechanisms, such as transcriptional upregulation of catalase, SOD1, and adiponectin, potentiation of the action of miR-33a, and direct or indirect inhibition of various profibrogenic mediators (DAMPs, osteopontin, etc.), proinflammatory cytokines (TNFα, IFN-γ, CCL2, IL-1, etc.), growth factors (VEGF, TGF-β1, etc.), and ROS. Abbreviations: CAT, catalase; CCL2, C-C motif chemokine ligand 2; COX, cyclooxygenase; DAMPs, damage-associated molecular patterns; PPARα, peroxisome proliferator-activated receptor alpha; ROS, reactive oxygen species; SOD1, superoxide dismutase 1.

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TABLE 1

Main preclinical studies of PPARα-related modulators for liver fibrosis

Agent	Models	Mechanisms	Effects	Refs.
Bezafibrate	Rat	Prevention of HSC activation		207
Feno fibrate	Human	Regulation of vanin-1		208
	Human hepatocytes/ Mice	Reduction of cholestasis		(14, 82, 129)
	Mice	Regulation of fatty acid metabolism		209
	Rat	Enhancement of catalase activity		55
	Rat	Modulation of inflammatory cytokines		210
	Mice	Reduction of hepatic iron accumulation		211
Pemafibrate	Mice	—		212
WY14643	Mice	Enhancement of catalase activity		66, 213
	Mice	Inhibition of insulin resistance		214
	Human hepatocytes	Control of catabolism of cytotoxic bile acids		(14, 129)
	Mice	Amelioration of hepatic cell death		215
PPARα/γ agonist				
Elafibranor	Mice/Rat	PPARa-dependent and -independent mechanisms		216
ZLY16	Mice	Enhancement of antioxidant enzymes activity		217
MHY2013	Mice	—		218
Triazo lone derivatives	Mice	—		219
PPARα/γ agonist				
Chiglitazar	Rat	Improvement of insulin resistance and dyslipidemia		220
Aleglitazar	Rat	Modulation of inflammatory cytokines		221
Saroglitazar	Mice/Rat	Improvement of insulin resistance, modulation of inflammatory cytokines ang adiponectin		222, 223
Pan-PPAR agonist				
Lanifibranor	Mice	Reduction of proinflammatory macrophages activation		224, 225
MBT1805	Mice	Reduction of cholestasis		226
Quadruple agonist				
RLA8	Mice	Reduction of lipotoxicity and oxidative stress		227
ZLY18	Mice	Reduction of lipotoxicity and oxidative stress		228
Chemical or oligonucleotide				
Oleoylethanolamide	Mice	Suppression of SMAD2/3 phosphorylation, α-SMA expression, and myofibroblast transformation		(186)
Pirfenidone	Mice	Activation of SIRTl/LKBl/pAMPK		229, 230
Melatonin	Mice	Regulation of circadian clocks		(75)
Ascorbic acid	Mice	—		231
Chicory seed extract	Rat/HepG2 cells	—		232

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Agent	Models	Mechanisms	Effects	Refs.
Syringic acid	Mice	Reduction of lipotoxicity		233
Glycyrrhizic acid	Mice	—		234
2,3,5,4'-tetrahydroxy stilbene-2-O-β-d-glu coside	Mice	Regulation of key regulators of lipid metabolism, inflammation, fibrosis, and oxidative stress		235
4-O'-methylhonokiol	Mice	Induction of MMPs, AEA, and NAEs and prevention of HSC activation,		(78)
Iso-alpha acids	Mice	Reduction of HSC activation and oxidative stress		236
Baicalin	Mice	Regulation of key regulators of lipid metabolism, proinflammatory cytokines, fibrosis markers		237
Betanin	Mice	Downregulation of SREBP-lc		238
Calycosin	Mice	Activation of farnesoid X receptor		239
Naringenin	Mice	Activation of hepatic SIRT1-mediated signaling cascades		240
Conophylline	Mice	Inhibition of hepatic TGF-β level		241
Curcumin	Rat	Regulation of oxidative stress, autophagy and epithelial-mesenchymal transition		242
Quercetin	Rat	Downregulation of the transcription of miR-21		243
Perfluorooctanoate	Mice	—		244
Alisol B 23-acetate	Mice	Activation of farnesoid X receptor		245
Telmisartan	Mice	Regulation of inflammatory- and fibrosis-related responses		246
Periostin antisense oligonucleotide	Mice	Downregulation of the hepatic periostin expression		247
CircRNA_0046367	HepG2 cells.	Reduction of miR-34a's inhibitory effect on PPARα		348
miRNA				
miR-21	Mice	Inhibition of PPARα expression		249
miR-27	Huh7 cells	Repression of PPARα signaling		(33)
miR-33a	Hepatic stellate cells LX-2	Regulation of HSCs trans differentiation and proliferation		(192)
miR-155	Mice	Enhancement of PPRE and PPARα binding and decreased		65
miR-540	Primary hepatocytes of mice	Inhibition of PPARα expression		250

 : positive effect on injury (), steatosis (), inflammation (), or fibrosis ().

 : neutral or non-available effect on injury (), steatosis (), inflammation (), or fibrosis ().

 : negative effect on injury (), steatosis (), inflammation (), or fibrosis ().

Abbreviations: PPRE, peroxisome proliferators response elements; PPARα, peroxisome proliferator-activated receptor alpha; Refs., references.

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TABLE 2

Main clinical outcomes of PPARα-related drugs for liver fibrosis

Agent	Clinical Trial # (Phase)	Comments	Effects	Refs.
PPARa agonist				
Bezafibrate	NCT01654731 (III)	In PBC patients (24 months): improved biochemical response, pruritus and liver stiffness.	◎◎●	259
	NCT02701166 (III)	In PSC and PBC patients (21 days): improved pruritus	◎◎◎	260
	NCT02937012 (III)	In PBC patients (3–12 months): improved cholestasis	◎●●	(261, 262)
Fenofibrate	NCT02781584 (II)	In NASH patients (2 weeks): improved hypertriglyceridemia	●◎◎	263
	NCT02354976 (II)	In NAFLD patients (12 weeks): reduced serum triglycerides	●◎◎	264
	NCT02891408 (I)	In NASH patients: completed, no results posted.	—	
	NCT00575042 (II)	In PBC patients (48 weeks): biochemical improvement	◎◎●	265
Pemafibrate (K-877)	NCT03350165 (II)	In NAFLD/NASH patients (72 weeks): reduced liver stiffness	◎◎●	266, 267
FGF21 mimetics				
Pegbelfermin (BMS-986036)	NCT02413372 (II)	In NASH patients (16 weeks): reduced hepatic fat content and liver transaminases, increased serum levels of adiponectin and improved lipid profde.	●●◎	268
	NCT03400163 (II)	In NASH patients: completed, no results posted.	—	
	NCT03445208 (I)	In NASH patients: completed, no results posted.	—	
	NCT03486899 (II) NCT03486912 (II)	In NASH patients (24, 48 weeks): improved fibrosis without NASH worsening.	◎●●	269
	NCT03674476 (I)	In NASH patients: completed, no results posted.	—	
Efruxifermin	NCT03976401 (IIa)	In NASH patients (16 weeks): improved hepatic fat content, NASH, and fibrosis.	●●●	270
PPARα/γ agonist				
Elafibranor	NCT03124108 (11)	In PBC patients (12 weeks): improved serum biochemical response and pruritus.	◎◎●	271
	NCT04526665(III)	In PBC patients: No results posted.	—	
	NCT01694849 (II)	In NASH patients (52 weeks): resolved NASH (F0-F3) without fibrosis worsening, improved cardiometabolic risk profile.	●●●	272
	NCT02704403 (III)	In NASH patients (72 weeks): terminated for not achieving NASH resolution without worsening fibrosis	◎◎◎	
PPARα/γ agonist				
Saroglitazar	NCT03061721 (II)	In NASH patients (16 weeks): improved ALT, liver fat content, insulin resistance and atherogenic disorders. Side effects: weight gain	●●●	273

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Agent	Clinical Trial # (Phase)	Comments	Effects	Refs.
	NCT03112681 (II)	In PBC patients (16 weeks): improved serum ALP (primary endpoint) and γGT levels Side effects: increase ALT in some patients	◎◎●	(274, 275)
	NASH (II)	Very small study demonstrating improved serum lipid and lipoprotein profiles; improvements in hepatocyte ballooning and steatosis; NASH resolution and fibrosis improvement were observed	●●●	(13)
	NCT03863574 (II)	In NASH patients: completed, no results posted.	—	
Pan-PPAR agonist				
Lanifibranor	NCT03008070 (II)	In NASH and F0-F3 fibrosis patients (24 weeks): improved biopsy-confirmed NASH, liver injury, inflammation, and fibrosis.	◎●●	276, 277
	NCT03459079 (II)	In NASH patients: No results posted.	—	225
	NCT04849728(III)	In NASH and F0-F3 fibrosis patients: No results posted.	—	

●●●: positive effect on steatosis (●), inflammation (●), or fibrosis (●).

◎◎◎: neutral or non-available effect on steatosis (◎), inflammation (◎), or fibrosis (◎).

Abbreviations: ALP, alkaline phosphatase; PPRE, peroxisome proliferators response elements; PPARα, peroxisome proliferator-activated receptor alpha; Refs., references.

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