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Review Article

An Overview of the Role of Peroxisome Proliferator-activated Receptors in Liver Diseases

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Abstract

Peroxisome proliferator-activated receptors (PPARs) are a superfamily of nuclear transcription receptors, consisting of PPARα, PPARγ, and PPARβ/δ, which are highly expressed in the liver. They control and modulate the expression of a large number of genes involved in metabolism and energy homeostasis, oxidative stress, inflammation, and even apoptosis in the liver. Therefore, they have critical roles in the pathophysiology of hepatic diseases. This review provides a general insight into the role of PPARs in liver diseases and some of their agonists in the clinic.

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Introduction

Nuclear receptors and transcriptional regulators called peroxisome proliferator-activated receptors (PPARs) have key roles in many physiological and pathological processes, especially energy homeostasis.[1] PPARs have three different subtypes: PPARα, PPARβ/δ, and PPARγ, which are located in chromosomes 22q13.31, 3p25.2, and 6q21.31 respectively.[2] PPARα (also called NR1C1(is present in tissues that catabolize fatty acids and it regulates inflammation and lipid metabolism.[3] PPARβ/δ (also called NR1C2) is less well known and is expressed in the heart, liver, kidneys, skeletal muscle, fat, skin, and gastrointestinal tract.[4,5] The PPARγ subtype (also called NR1C3) improves skeletal muscle insulin sensitivity while causing fat storage and lipogenesis in both white and brown adipose tissue. It is also expressed in hepatic stellate cells (HSCs).[6] Target genes for the three PPAR alpha, beta/delta, and gamma receptor isoforms are distinct but also overlapping.[7] Although PPARs naturally and primarily appear in the nucleus, they actively shuttle between the nucleus and cytoplasm, regulated by different PPAR ligands.[8]

Notwithstanding their roles in lipid and glucose metabolism,[9] growing findings suggest that PPARs function in the modulation of other processes such as inflammation and innate immunity.[10] Fatty acids (FAs), eicosanoids, and phospholipids produced by cellular FA metabolism or dietary lipids are natural ligands of PPARs.[11] Upon ligand binding, PPARs and retinoid X receptors (RXRs) as major coactivators, create heterodimers, bind to peroxisome proliferator response elements, and influence the expression of downstream target genes.[12,13]

The liver is the main organ responsible for regulating lipid and glucose homeostasis through controlled biochemical, signaling, and cellular pathways.[14] The production of plasma proteins, clotting factors, bile, and the excretion of metabolic waste products are some other liver functions.[15,16] Liver diseases imply a broad range of liver disorders, involving over 2 million individuals worldwide each year and affecting other body-system functions, lifestyle, and lifespan.[17] Given that PPARs are currently considered important factors in hepatic physiological and pathological processes, investigation of their role in liver diseases seems very useful. Therefore, the objective of this review is to present an overview of PPAR functions in health and in liver diseases.

Physiological function and regulation of PPARs

PPARs are one of the main sensors and regulators of lipid metabolism. In this regard, PPARα is a significant target for fibrate hypolipidemic drugs, implicated mainly in the catabolism of FAs and their oxidation in the heart, muscle, liver, kidney, small and large intestine.[18] It also causes glucose homeostasis and insulin resistance. PPARα agonists reduce renal blood pressure by interfering in the renin angiotensin system and provide renal vasodilatation by promoting the expression of endothelial nitric oxide synthase (commonly known as eNOS) in endothelium.[19,20] PPARα participates in cardiomyocyte metabolism and protects against cardiac inflammation and infarction.[21] In the liver, PPARα activation promotes FA oxidation and thermogenesis and PPARγ promotes energy storage by increasing lipogenesis and adipogenesis. PPARα is a nutrient-sensing nuclear receptor that has important effects in fasting. Food restriction increases

Keywords: Liver; Endoplasmic reticulum stress; Nonalcoholic fatty liver disease; PPARα; PPAR; PPARβ/δ.

Abbreviations: FAs, fatty acids; FXR, farnesoid X receptor; HBV, hepatitis B virus; HDL, high-density lipoprotein; KLF, Krüppel-like factor; LXR, liver X receptor; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NF-κB, nuclear factor kappa light-chain enhancer of activated B cells; PCG-1, PPARγ coactivator-1; PPARs, peroxisome proliferator-activated receptors; RXR, retinoid X receptor; SREBP, sterol regulatory-element binding protein; TFEB, transcription factor EB; UCP1, uncoupling protein-1.

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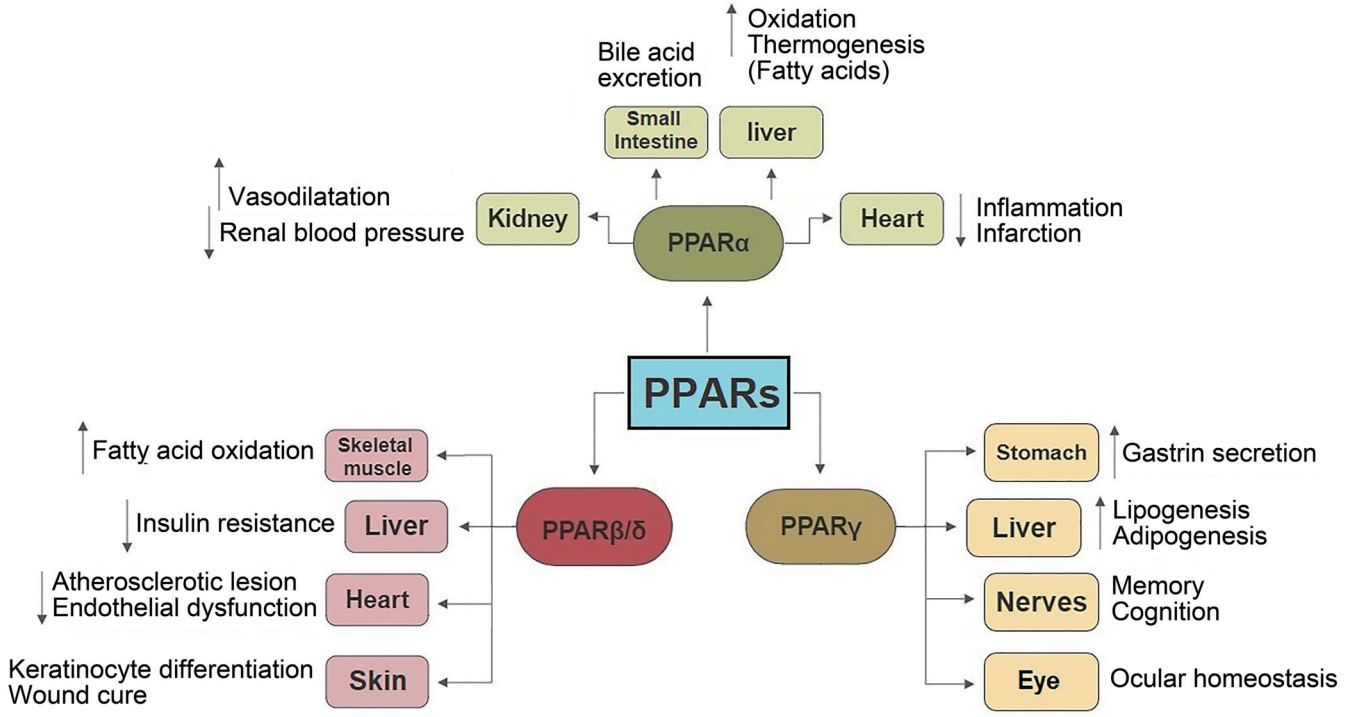

Fig. 1. Function of PPARs in different tissues in physiological conditions. PPARs, peroxisome proliferator-activated receptors.

PPARα expression,[22] and in fasting, PPARα is upregulated and induces some transcription factors such as fasting induced adipose factor (commonly known as FIAF) and fibroblast growth factor (commonly known as FGF) 21, which increase circulating free FAs and ketone bodies to supply energy and prevent hypoglycemia.[23–25] Adipose triglyceride lipase (commonly known as ATGL) is a key enzyme here and its absence leads to a decrease in PPARα production.[26] In feeding, PPARα increases the maturation of the transcription factor sterol regulatory-element binding protein (SREBP) 1c.[27] PPARs are involved in glycerol metabolism as an important substrate for hepatic glucose synthesis. Accordingly, PPARα controls glycerol metabolism in the liver, and PPARγ regulates glycerol metabolism in adipose tissue.[28] Additionally, PPARα activates Vanin-1, which is a prominent PPARα-dependent regulated gene in the liver and decreases hepatic steatosis through change in inflammation and oxidative stress pathways.[29] PPARα also regulates bile acid metabolism and excretion.[30]

PPAR-β/δ subtype is involved in FA oxidation, keratinocyte differentiation, wound cure, and adipogenesis.[31] The PPAR-β/δ is mainly expressed in the macrophages and skeletal muscle.[32] Following activation, PPARβ/δ inhibits interleukin 6 (commonly known as IL6) induced insulin resistance by inhibiting the signal transducer and activator of the transcription 3 (commonly known as STAT3) pathway in adipocytes. However, this pathway is overactivated in PPARβ/δ-null mice compared with wild-type animals.[33] PPARδ controls the diurnal expression of lipogenic genes in the dark/feeding cycle that peaks with nocturnal feeding and leads to muscle lipid oxidation. This results from coordination between the liver and muscle in metabolic functions. PPARβ activation is accompanied by an increase in circulating high-density lipoprotein (HDL) levels and chemoattractant signaling suppression in the aorta, which reduces atherosclerotic lesion formation.[34] The overexpression of PPARβ/δ in cardiac cells also leads to an increase of glucose metabolism and a decrease of lipid accumulation, and it is associated with cardiac endothelial dysfunction via reducing oxidative stress.[35]

PPARγ expression is often observed in the spleen, the large intestine, and brown and white adipose tissue. Of the two PPARγ isoforms, PPARγ1is expressed in the liver and other tissues. The PPARγ2 isoform is expressed exclusively in adipose tissue, where it controls adipogenesis and lipogenesis. The PPARγ2 isoform can inhibit lipotoxicity by promoting adipose tissue extension and expanding lipid-buffering size in peripheral organs.[36] PPARγ activity in adipocytes directly regulates adipocytokine secretion in peripheral tissues,[37] and in PPARγ1 and 2-knockout mouse adipocytes, fat accumulation decreases and glucose tolerance improves.[38] The PPARγ1 isoform is expressed in many dendritic cells where it has a role in memory and cognition.[39] It has been shown that the macrophage activation of PPARγ suppressed the production of pro-inflammatory cytokines, such as tumor necrosis factor alpha (commonly known as TNFα), IL1β and IL6.[40] PPARγ was also shown to increase gastrin secretion in the stomach.[20] The physiological range of sex hormones, including testosterone, estradiol, and dihydrotestosterone, also downregulates PPARγ expression and function.[41] Escandon *et al*.[42] reported that PPARs have important roles in ocular homeostasis (Fig. 1).

PPARs and other transcription factors

As shown in Figure 2, RXRs are the main nuclear receptor to react with PPARs. After ligand binding, PPARs form heterodimers with nuclear RXR. This compound adheres to the peroxide proliferator response element in DNA and changes gene expression and synthesis of new proteins in the cells.[43] Another nuclear receptor that reacts with PPARs is the P65

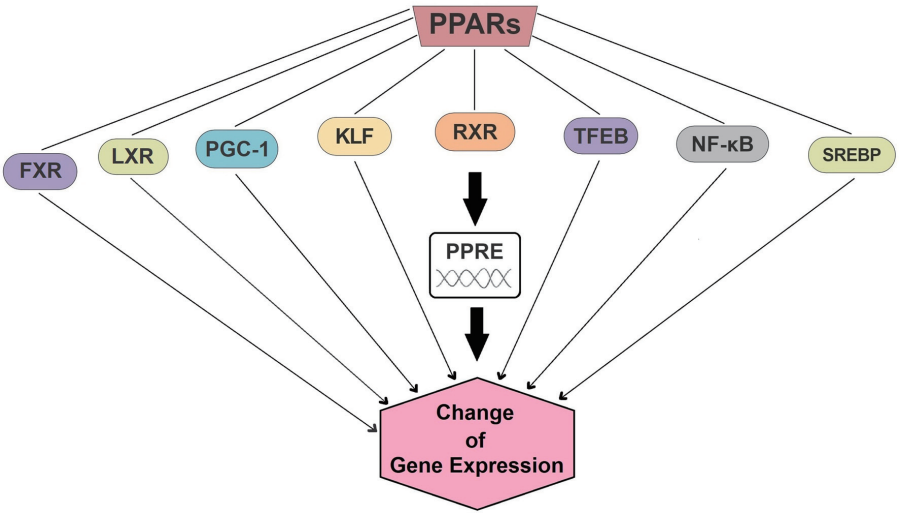

Fig. 2. Interactions of PPARs and other transcription factors. FXR, Farnesoid X receptor; LXR, Liver X receptor; PCG-1, PPARγ coactivator-1; KLF, Krüppel-like factor; RXR, Retinoid X receptor; TFEB, transcription factor EB; NF-κB, nuclear factor kappa light-chain enhancer of activated B cells; SREBP, sterol regulatory-element binding protein.

subunit of nuclear factor kappa light-chain enhancer of activated B cells (NF-κB). The PPAR/NF-κB interaction orchestrates some metabolic-based inflammatory responses.[44] In the heart, PPARs attenuate NF-κB activity and have antifibrotic and cardiac remodeling effects.[45,46]

The Krüppel-like factor (KLF) family includes zinc finger-containing transcription factors that are involved in many cell processes, including metabolic homeostasis.[47] A recent study in skeletal muscle showed that KLF15 had a critical role in metabolic reinforcement through its interactions with PPARδ, suggesting that KLF15 facilitated PPARδ-mediated transcription.[48] The antimycobacterial responses of PPARα are another important function of this transcription factor that follows activation of transcription factor EB (commonly known as TFEB). TFEB is a protein coding gene associated with various diseases, such as renal cell carcinoma, Xp11.2 translocation and pycnodysostosis.[49] Kim *et al*.[50] reported that during mycobacterial infection, PPARα deficiency resulted in an exaggerated inflammatory response and increased bacterial load. PPARα activation during mycobacterial infection promoted FA β-oxidation and lipid catabolism in macrophages.[50]

Liver X receptors (LXRs) and SREBP-1c are two other factors that interact with PPARs and are key regulators of liver normal functions.[51,52] LXRs are as orphan nuclear receptors that control intracellular cholesterol levels and bile acids. Yoshikawa *et al*.[53] showed that LXRs activation led to signaling repression by decreasing PPAR/RXR heterodimerization in the liver.[53] The SREBP-1c transcription factor also regulates *de novo* lipogenesis in the liver in response to increases of insulin.[54] SREBP-1c enhances the transcription and activity of PPARγ.[55] On the other hand, PPARα represses SREBP-1c/LXR activity.[56]

Peroxisome proliferator-activated receptor gamma coactivator-1 (PGC-1) is a family of transcriptional coactivators that interact with PPARs. For example, PGC-1α activates PPARα in mitochondrial FA oxidation, and PGC-1α/PPARγ interaction promotes the expression of encoding aP2, uncoupling protein-1 (UCP1), and glycerol kinase genes.[57] Farnesoid X receptor (commonly known as FXR) is a transcriptional factor that interacts with PPARs, especially PPARα. FXR is an upstream protein that activates PPARα expression. They both activate FA oxidation and triglyceride metabolism and decrease the expression of SREBP-1c. They also induce liver autophagy in mice with steatohepatitis.[58,59]

PPARs in liver diseases

Role of PPARs in nonalcoholic fatty liver

In Western countries, nonalcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease.[60] NAFLD includes a broad spectrum of liver disorders such as simple steatosis, nonalcoholic steatohepatitis (NASH) and liver fibrosis.[61] It may progress to cirrhosis and hepatocellular cancer.[62] All PPAR isotypes control the activation of HSCs and inflammation and are closely related to glucolipid metabolism in NAFLD.[63] Because of the association of NAFLD with obesity and hyperglycemia and the important role of PPAR in the transcriptional regulation of glucose and lipid metabolism, their ligands are good options as therapeutic agents.[64] It has been demonstrated that PPAR activation prevented NASH development by increasing the release of adipokines such as adiponectin and stimulating the expression of genes related to beta oxidation and decreasing inflammation and oxidative stress.[63,65,66] As PPARα is a nutritional sensor and enables the modification of FA oxidation, lipogenesis, and ketone body synthesis rates in response to feeding and fasting, its hepatic expression falls when dietary lipid intake is excessive.[67] After PPARα/RXR dimerization and entrance into the nucleus, beta-oxidases, including carnitine palmitoyltransferase 1 (commonly known as CPT-1), a key enzyme in lipolysis, were upregulated and allowed FAs to move to the mitochondrial matrix for further metabolism.[58] PPARα also induced FA binding protein 1 (commonly known as FABP) expression and thereby inhibited HSCs activation, resulting in NASH improvement.[68] Deficient mice (i.e. PPAR$^{-/-}$) in either the whole body or only hepatocytes, developed steatosis and gained weight with overexpression of lipid synthesis-related genes, and increased inflammation with both control and high-fat diets.[22,69] This could well confirm the unique role of PPARα in lipid catabolism both in the hepatocytes and extrahepatic cells. Fibrates are considered weak PPARα agonists and some studies have demonstrated an improvement in the biochemical or histological parameters affected by fibrates

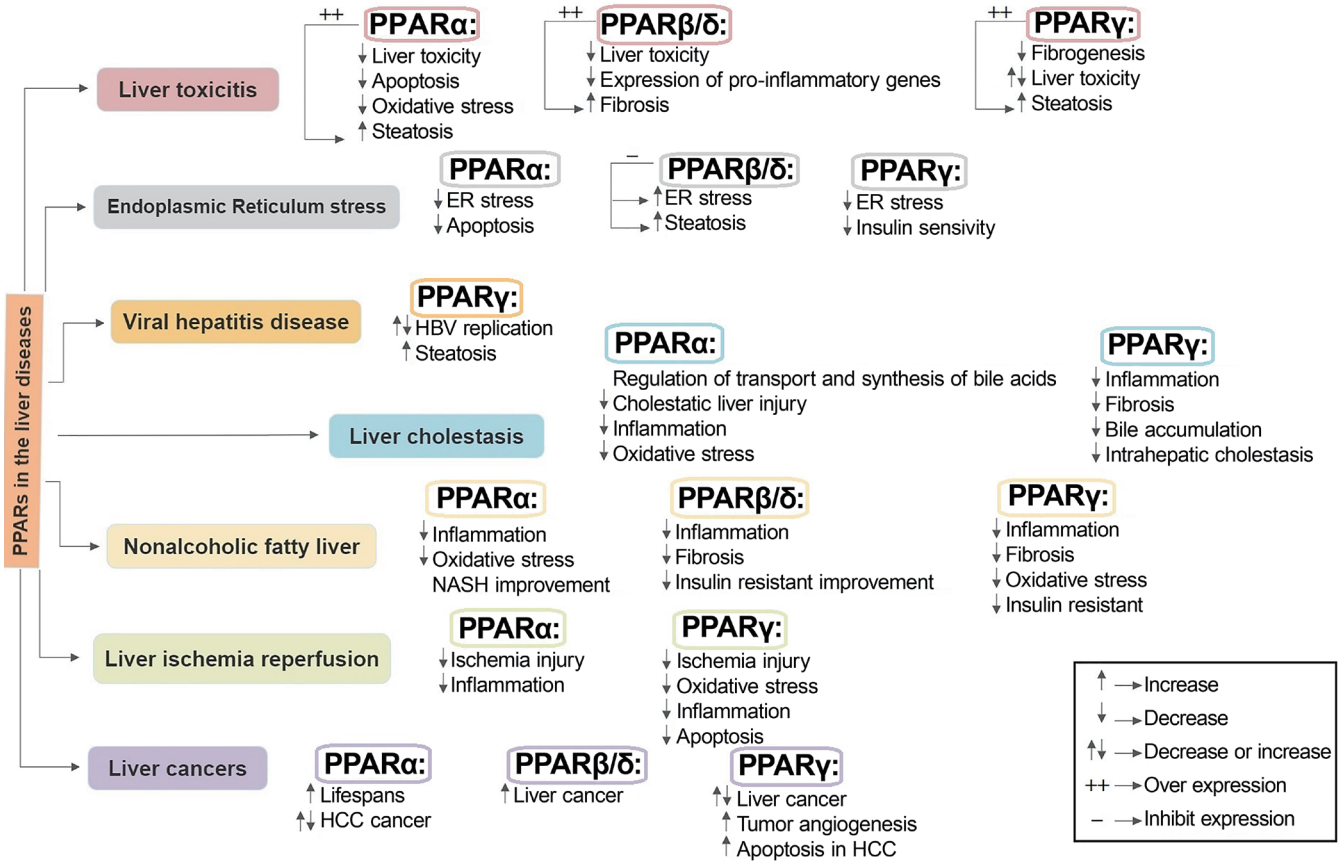

Fig. 3. Role of PPARs in different liver diseases. ER, endoplasmic reticulum; HCC, hepatocarcinoma cancer; NASH, nonalcoholic steatohepatitis; PPARs, peroxisome proliferator-activated receptors.

in NAFLD patients.[70,71] Although there is no doubt about the beneficial effects of PPARα in attenuating NAFLD, their agonists have some side effects and their clinical application in NAFLD should be further studied.

In addition to hepatocytes, PPARβ/δ is expressed in Kupffer cells and HSCs, suggesting its potential role in inflammation and fibrosis. Hepatic PPARβ/δ activation not only improves NAFLD through lipolysis related pathways but also reduces hepatic steatosis through autophagy-mediated FA oxidation.[72] GW501516 and GW0742 are PPARβ/δ agonists that were shown to ameliorate obesity and insulin resistance and reduce serum triglycerides and low-density lipoprotein cholesterol (LDL-C) in rats and humans.[73] According to the available clinical trials for the safety of PPARβ/δ agonists, it has been determined that short-term treatment with these drugs in humans is safe and generally tolerable.[74]

As previously mentioned, PPARγ is significantly expressed in latent HSCs; nevertheless, it is repressed during the fibrosis process, prevents the activation of the HSCs, and lowers the amount of collagen deposition during liver fibrogenesis. Therefore, PPARγ might be a useful target for the treatment of liver fibrosis.[75] Despite its role in hepatic fibrosis attenuation, PPARγ is involved in *de novo* lipogenesis and FFA import. In hepatocytes, PPARγ induced adipocyte protein 2 and a cluster of differentiation (CD) 36-mediated FFA uptake and promoted FA synthase (commonly known as FAS) and acetyl-CoA carboxylase 1 (commonly known as ACC1) activity.[76] PPARγ has additional roles in NAFLD-related processes, including insulin resistance, inflammation, oxidative stress, and endoplasmic reticulum (ER) stress.[77] in NAFLD patients and laboratory animals, the expression levels of hepatic PPARγ are higher[64] and are significantly associated the initiation of NAFLD and hepatocyte-specific PPARγ expression.[78] However, partial PPARγ activation has benefits, mostly brought about by increased adiponectin levels, decreased leptin levels, and insulin resistance improvement.[64] Pioglitazone is a PPARγ agonist that can raise the plasma adiponectin levels by acting as an anti-inflammatory and antifibrotic agent (Fig. 3).[79] Overall, all types of PPARs have important roles in NASH improvement and steatosis and inflammation restriction. Nevertheless, the effect of PPARα is exclusive. However, it needs more appropriate agonists in patients with NAFLD.

Role of PPARs in ER stress

The ER is a large, dynamic structure with numerous roles in the cell, including lipid metabolism, protein synthesis, and calcium storage.[80] After disturbance in the ER, ER stress occurs and correct protein folding is disrupted.[81,82] The evidence shows that prolonged ER stress is linked to the development and progression of various diseases, including neurodegeneration, type 2 diabetes, atherosclerosis, cancer, and liver diseases.[83] Inhibition and activation role of PPARα has been shown to be involved in ER stress.[66] PPARα is a key molecule in the functional conversion of ER stress. PPARα inhibition by small interfering RNA (commonly known as siRNA)-promoted cell injury in mild ER stress, and PPARα activation reduced cell apoptosis in severe ER stress.[84] Recently, Van der Krieken *et*

al.[85] reported a link between ER stress, PPARα activation, and inhibition of apolipoprotein A-I Transcription. They showed that activating PPARα increased apoA-I transcription and bromodomain and extra-terminal domain (commonly known as BET) protein inhibitors, worsened ER stress, and decreased apoA-I transcription. ER-stress-mediated reduction in apoA-I transcription was most likely partly mediated via the inhibition of PPARα mRNA expression. In addition, BET inhibition increased apoA-I transcription.

In a study by Zarei *et al*.[86] PPARβ/δ knockout led to hepatic ER stress, the induction of activating transcription factor 4 (AFT4) and eukaryotic initiation factor 2 alpha (eIF2α) expression, upregulation of ER stress-induced very low-density lipoprotein receptor, and liver steatosis in mice. Magnesium lithospermate B, a biological agonist of PPARβ/δ, suppressed liver ER stress and increased insulin level and insulin receptor substrate-1 (commonly known as IRS-1).[87] In hepatic ER stress, increased proline-rich, extensin-like receptor kinase expression (an important sensor of ER stress) led to eIF2α downregulation and decreased PPARγ through CCAAT-enhancer-binding protein (commonly known as C/EBP)/PPARγ signaling.[88] PPARγ also attenuated ER stress by activation of the PPARγ/Nogo-B receptor (commonly known as NGBR) pathway, which improved liver insulin sensitivity.[89] These studies demonstrate that at least one of the pathways through which both PPARβ/δ and PPARγ ameliorate liver ER stress is the downregulation of eIF2α and C/EBP, thereby promoting liver function and insulin sensitivity. Several studies (Fig. 3) have shown that PPARα/γ agonists improved liver function via lowered ER stress.[90,91]

Role of PPARs in infectious hepatitis

Infectious hepatitis is one of the most common causes of hepatitis and results from viral and bacterial infection.[92] Hepatitis A, B, C, D, and E are the five primary hepatitis virus subtypes. Each kind of viral hepatitis is caused by a distinct virus.[93] According to an old report, PPARγ can block hepatitis B virus (HBV) replication, hepatitis B surface antigen, and hepatitis B e antigen *in vitro*.[94] However, there are also conflicting newer findings. It was shown that bezafibrate, fenofibrate, and rosiglitazone promoted HBV replication. It has been recommended that HBV viral load be managed and regimens might need to be altered, with the addition of an antiviral medication when HBV-infected individuals are treated with PPAR agonists for metabolic illnesses.[95] In addition, PPARγ causes hepatic steatosis by activating the HBV X protein.[94] Overexpression of the FABP1 gene, which is controlled by PPARα, C/EBPα, and hepatocyte nuclear factor (HNF) 3β, causes the hepatic fat accumulation brought on by HBVx.[96] It has been demonstrated that during bacterial hepatitis, PPARα activates and leads to a shift from glucose to lipid utilization, and an increase of ketone bodies, as a result helping in survival promotion.[97] This effect is produced through hepatic FGF21 overexpression, which maintains thermogenesis, energy expenditure, and cardiac function. However, the opposite occurs in influenza infection.[98,99]

On the other hand, hepatitis C virus (commonly known as HCV) infection impairs PPARα and PPARγ mRNA expression,[100] and coinfection with human immunodeficiency virus (commonly known as HIV) significantly reduces the expression of the mRNA both receptors through IL1β and decreases HSC activation. However, black patients experienced significantly less suppressive effects of viruses.[101,102] Other studies showed that via PPARγ, genotype 3a of the HCV core protein elevated suppressor of cytokine signaling (SOCS) 7 expression in Huh-7 cells. In contrast to other members of the SOCS1 and SOCS3 under study, whose expression is controlled by STAT3 activation, SOCS7 expression seems to be controlled by PPARγ.[103,104] another study found that PPARα formed a complex with heat shock protein 90 and X-associated protein 2 (commonly known as XAP2), and that XAP2 was active as a repressor. PPARα is consistently linked to other proteins in tissue extracts and is the nuclear receptor that associates with XAP2 hepatitis virus B (Fig. 3).[105] In this context, there are contradictory results about PPARs effects and further studies are required.

Role of PPARs in liver toxicity

Synthetic chemicals and environmental pollutants can interrupt normal liver homeostasis and provide hepatotoxicity. Hepatotoxicity relates to different roles of PPARα, PPARγ, and PPARβ.[106] Studies have shown that PPARα activation prevents acute liver toxicity.[106,107] Cell death might be prevented by the activation of PPARα, thereby inducing resistance in hepatocytes and/or induction of death protein inhibitors in the dead or dying cells.[108] Another study reported that fibrates (PPARα activators) prevented acetaminophen hepatotoxicity in mice.[109] Acetaminophen-induced hepatic hypoxia also inhibits PPARα expression to amplify hepatotoxicity and oxidative stress.[110] Peraza *et al*.[111] reported that activation of PPARα modulated liver toxicity by interfering with aryl hydrocarbon receptor (commonly known as AhR)-dependent signaling. Ernst *et al*.[112] reported that amiodarone-induced hepatic steatosis in mice was associated with an upregulation of target genes modulated by PPARα. As amiodarone does not stimulate PPARα directly, target-gene induction may reflect a compensatory reaction countering some harmful effects of amiodarone. The protective influence of PPARα on reducing amiodarone-induced hepatic toxicity was shown with the aforementioned results.[112] PPARα activation was also shown to protect against carbon tetrachloride and cadmium-induced liver toxicity.[113] The aforementioned and similar studies have demonstrated the amelioration of PPARα of hepatotoxicity mediated by diverse anti-inflammatory pathways.

PPARγ activation induces mild liver toxicity but attenuates liver fibrogenesis.[106] Troglitazone and rosiglitazone are PPARγ agonists that is reported to induce mild liver toxicity in patients.[114] Despite the PPARγ activation in hepatotoxicity, PPARγ ligand treatment attenuates fibrogenesis. The attenuation of PPARγ inhibits the activation of HSCs and it results in a decrease in fibrogenic gene expression, including collagen and α-smooth muscle actin.[115] Hepatotoxicity is one of the most studied activities of PPARγ agonists.[111] Although one PPARγ ligand can cause liver toxicity, recent findings suggest that another PPARγ ligand can protect against liver damage.[111] Although, thiazolidinediones, which are PPARγ agonists, can cause hepatotoxicity,[106] it was shown that the induced orchestrated activation of PPARα and PPARγ reprogrammed hepatic macrophage polarization, thereby affecting lipid homeostasis in mice's liver.[116] Lipid droplets emerge when PPARγ is ectopically overexpressed in hepatocytes. For example, the overexpression of PPARγ2 following adenovirus exposure increased hepatosteatosis in mice.[117] Bruno *et al*.[118] reported that methoxy eugenol, a molecule found in nutmeg and Brazilian red propolis, attenuated carbon tetrachloride-induced liver fibrosis through the activation of PPARγ. Despite the positive role of PPARα in the attenuation of hepatic toxicity, activation has dual effects of promoting liver toxicity on one hand and attenuates liver fibrosis through HSC suppression on the other. Further studies are needed to clarify the aforementioned effects. PPARβ/δ preventive or therapeutic role for alcoholic liver disease might be similar in hepatotoxicity. In the liver, PPARβ/δ might influence the inflammatory activity of Kupffer cells. The PPARβ/δ subtype, possibly

by downregulating expression of proinflammatory genes, is protective against liver toxicity induced by environmental chemicals.[119] Nevertheless, PPARβ activation promotes the progression of liver fibrosis (Fig. 3).[106]

Role of PPARs in liver cancer

Hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma are the two main kinds of primary liver cancer. Less common malignancies include angiosarcoma, hemangiosarcoma, and hepatoblastoma. HCC develops from hepatocytes, and intrahepatic cholangiocarcinoma starts in the bile ducts.[120,121] It should be noted that primary liver cancer therapy and prognosis are greatly influenced by the severity of underlying liver cirrhosis.[122] As PPARs targets have been identified in liver disorders, study of new therapeutic alternatives in liver cancer has taken a big step.[52] PPARs regulate the cell cycle and metabolism, thus they have special role in carcinogenesis, However, it is not yet apparent which PPAR subunits promote or inhibit cancer.[123]

Although in HCC, the nuclear expression of PPARα is lower than in normal liver tissue and HCC patients who have a higher nuclear and cytoplasmic expression of PPARα have longer lifespans.[124] When a PPARs agonist (e.g., nafenopin) was administered to mice or rats for an extended period, it was observed that hepatocellular cancer or hepatomegaly developed.[125] It has been reported that by eliminating PPARα, HCC caused by fatty liver and hepatomegaly was inhibited in HCV core transgenic mice.[126] Vacca *et al*.[127] reported that Hepa1-6 hepatoma cell proliferation was decreased by the PPARβ/δ agonist GW501516.[127] Adenomatous polyposis coli (commonly known as APC) is a tumor suppressor that inhibits PPARβ/δ transcription by controlling the β-catenin/Tcf-4 pathway. Therefore, PPARβ/δ activity might be elevated as a result of APC/β-catenin mutations.[4] Sorafenib-resistant HCC cell metabolic programming was reversed by inhibiting PPARβ/δ activity, a crucial regulator of glutamine metabolism. Eventually, these cells developed sorafenib sensitivity.[128]

In early cancers, PPARγ expression is markedly downregulated in tumor tissue relative to nontumor tissue.[129] It has been determined that PGC-1α's metastasis suppressor action is dependent on PPARγ because PGC-1α inhibits the Warburg effect via regulating the WNT/β-catenin/PDK1 axis.[130] Additionally, the intrinsic and extrinsic cell interactions in HCC have demonstrated the interaction between PPARγ, HSCs, and the fibrogenic microenvironment. In the premalignant milieu, these interactions induce growth arrest, cell senescence, and cell clearance.[109] Contrary to the above findings, patients with promoted HCC highly express PPARγ, which can be used as a prognostic indicator.[131] PPARγ is intrinsically active in tumor cells, elevates vascular endothelial growth factor A (commonly known as VEGF-A) transcription, and results in promoting myeloid-derived suppressor cell proliferation and CD^{8+} cell dysfunction. In orthotopic and spontaneous HCC models, a specific PPARγ antagonist (pembrolizumab) changed the suppressive tumor microenvironment into an immunostimulatory one and made tumors more responsive to anti- programmed death-ligand 1 (commonly known as PD-L1) therapy.[132] Finally, it is generally stated that as an adjunctive therapy, activation of PPARα and PPARγ sensitizes tumor cells to traditional anticancer therapies used in HCC.[52]

Feng *et al*.[133] demonstrated that simvastatin blocked the hypoxia inducible factor-1 alpha (commonly known as HIF-1α)/PPARγ/pyruvate kinase muscle 1 (commonly known as PKM2) axis, reducing PKM2-mediated glycolysis and boosting the expression of apoptotic markers in HCC cells, making them more susceptible to sorafenib treatment. Similarly, telmisartan, a partial agonist of PPARγ, increased tumor sensitivity to sorafenib by modulating the extracellular signal-regulated kinase 1/2 (commonly known as ERK1/2), transforming growth factor-β activated kinase 1 (commonly known as TAK1), and NF-κB signaling axis.[134] Another study found that the cyclic isoprenoid β-ionone (βI), which has been proposed as a possible chemotherapeutic drug when combined with sorafenib, controlled the expression of PPARγ via RXR.[135] PPAR activity in hepatic cancers differ. PPARα usually has a promoting action but PPARγ and PPARδ have mostly tumor suppressive activity. Overall, PPARs promote or suppress liver cancers depending on the PPAR type, cancer type, and tumor stage (Fig. 3).

Role of PPARs in liver cholestasis

Reduced bile formation causes a condition called cholestasis. This leads to a reduction in membrane fluidity and an increase in membrane cholesterol content. Cholestasis biochemical features reflect the maintenance of bile ingredients in the serum, such as bilirubin, bile acids, and cholesterol.[136] There are limited studies to investigate the mechanism of the protection of PPARs against cholestasis. Currently, PPARs, owing to their expression in different hepatic parenchymal and nonhepatic parenchymal cell compartments, are of great interest for the treatment of cholestasis. PPAR agonists also have benefits in cholestasis (e.g., bezafibrate and fenofibrate). Bezafibrate has a similar affinity for the PPARα, PPARγ, and PPARδ. Fenofibrate is a PPARα-specific agonist.[137]

PPARα effectively reduces cholestatic liver injury, thereby improving patient physiological status by the anti-inflammatory effects. During cholestasis, the activation of PPARα has emerged as a novel goal for controlling the transport and synthesis of bile acids.[136] Potential treatments for cholestasis by PPARα mainly involve the reduction of the bile acid pool size in the liver and regulation of damage caused by cholestasis.[136] Li *et al*.[138] showed that a deficiency of PPARα exacerbated liver injury in cholic acid-induced cholestasis and the activation of PPARα signaling suggested that it protected against cholestatic liver damage. A recent study revealed that fenofibrate, which activates PPARα reversed bile acid metabolism disorders, improved mitochondrial FA beta oxidation (commonly known as β-FAO), and decreased the inflammation and oxidative stress of cytokines in alpha-naphthyl isothiocyanate (commonly known as ANIT)-induced cholestasis.[139] The results collectively confirm that PPARα agonists have potential as therapeutic agents for cholestatic liver damage. The importance of PPARα in controlling bile acid balance and treating inflammation during cholestasis has led to new ideas for managing the condition, although its primary physiological function is to regulate the metabolism of glucose and other energy sources.[136] Fenofibrate protection against cholestasis-induced liver damage depends on the fenofibrate dose and PPARα, and is mediated by inhibiting c-Jun N-terminal kinase (JNK) signaling.[141] It was demonstrated that formononetin inhibited the ANIT-induced inflammatory response by PPARα-dependently inactivating the JNK inflammatory pathway.[141] Dai *et al*.[142] reported that PPARα activity effectively protected mice against cholestasis-induced liver injury via inhibiting JNK signaling. In the aforementioned studies, JNK signaling is supported as a pathway for the attenuation of cholestasis-induced liver injury.

PPARγ protects against injury from cholestatic liver disease. The activation of PPARγ by tectorigenin also inhibits hepatic inflammation and bile accumulation and alleviates intrahepatic cholestasis.[143] A recent study showed that a PPARγ agonist (formononetin) improved intrahepatic cholestasis and cholestasis associated dyslipidemia induced

by α-naphthyl isocyanate.[144] In intrahepatic cholestasis of pregnancy, the production of reactive oxygen species could be inhibited by PPARγ and lead to a decrease in the level of inflammation through NF-κB downregulation, which might be a mechanism for intrahepatic cholestasis of pregnancy (Fig. 3).[145] The results of the above studies show the potential ability of PPARγ and PPARα to ameliorate hepatic cholestasis and therefore to limit disease development.

Role of PPARs in liver ischemia-reperfusion

Hepatic ischemia-reperfusion injury (IRI) is a major side effect of liver surgery and liver transplantation and a significant contributor to liver dysfunction.[146] Hepatic ischemia-reperfusion-induced acute inflammation resulted in the production of reactive oxygen species and release of inflammatory cytokines that damaged liver cells and caused organ failure.[147] The interactions of hepatocytes, Kupffer cells, neutrophils, macrophages, sinusoidal endothelial cells, and platelets are among the many intricate and varied mechanisms that make up the pathophysiology of hepatic IRI.[148]

By activating PPARα and PPARγ, it has been shown that PGC-1 protects the liver against hepatic IRI.[149] Additionally, curcumin has been shown to increase PPARα/γ and cyclic adenosine monophosphate (commonly known as CAMP)-responsive element binding protein (commonly kmown as CREB) 1, which are both involved in hepatic ischemia/reperfusion.[150,151] Increase in the expression of antioxidant enzymes and decrease in NF-κB activity caused by the administration of WY-14643, a specific agonist of PPARα, improved the antioxidant and anti-inflammatory defense system, it may have potential as a clinical treatment of liver IRI.[152] Massip-Salcedo *et al*.[153] reported that activation of PPARα in rats with steatotic livers and undergoing IRI, reduced the harmful effects of adiponectin. In liver IRI, N-3 polyunsaturated FA supplementation induced PPARα activation and PPARα interaction that had anti-inflammatory consequences.[154] PPARγ protection against hepatic IRI was reported to be mediated by the NF-κB pathway.[155] In general, the protective effects of PPARγ have been widely reported and include reducing oxidative stress, inhibiting inflammatory responses, and antagonizing apoptosis.[156] PPARγ is associated with various physiological pathways and has an important role in acute IRI of the liver through the AMP-activated protein kinase (AMPK)/mammalian target of rapamycin (commonly known as mTOR)/autophagy pathway. PPARγ is thus a regulator and potential therapeutic target that can reduce liver damage in IRI.[157] PPARγ activation decreases IRI and pro-inflammatory NO^+ Kupffer cells by attenuating the pro-inflammatory character of Kupffer cells and IRI; therefore it can become a significant strategy to modify outcomes in liver surgery (Fig. 3).[158] Interaction between CREB1 and PPARα seems to have the main role in the improvement of IRI. However, PPARγ uses AMPK and mTOR signaling pathways. Nevertheless, in both PPARs, NF-κB is a common transcription factor.

Role of clinical PPAR agents in liver disease

Fibrates are considered the most prevalent PPARα agonists. In a randomized clinical trial, pemafibrate, which is a selective PPARα agonist, did not reduce liver fat in patients with NAFLD, but significantly reduced liver stiffness based on magnetic resonance elastography (MRE).[159] In another clinical study, pemafibrate was assessed in NAFLD and atherosclerosis (AS), and was reported that pemafibrate was superior to conventional fibrates and might even be used for chronic kidney disease.[160]

The clinical use of fibrates has been associated with side effects, including liver damage and elevated creatinine levels.[161,162] Although a clinical trial on fibrates has shown negative results for the prevention of atherosclerotic cardiovascular disease,[163] another clinical trial conducted in Japan confirmed the superior effects of pemafibrate on lowering triglycerides and increasing HDL-cholesterol (HDL-C).[162] A review reported that combination therapy with fenofibrate, another PPARα agonist, and a statin in individuals with cardiovascular disease was safe and reduced dyslipidemia.[164] Generally, in individuals at risk for cardiovascular disease, fibrate medication decreases nonfatal coronary events, atherostatic plaque, and dyslipidemia, but often does not decrease death.[165] Another trial revealed a decrement of hepatocellular ballooning grade without changes in steatosis, lobular inflammation, and fibrosis in nonalcoholic fatty liver patients treated with fenofibrate.[166]

We did not find significant clinical studies of the effects of PPARβ/δ agonists (i.e. GW501516 and GW0742) on the liver. Although there are few clinical trials evaluating the safety of PPARβ/δ agonists in other tissues, these medications appear to be safe and well-tolerated when administered to humans, at least for brief periods.[167] It is interesting that AMPK activation is a key component of the majority of PPAR β/δ agonist antidiabetes activities.[74,168] It is also reported that growth differentiation factor 15 (commonly known as GDF15) activated AMPK to mediate the metabolic effects of PPARβ/δ.[169] Although, there are some positive results on ameliorative effects of fibrates in liver diseases, it needs to more studies to confirm.

Thiazolidinediones, which are selective agonists for the PPARγ, are currently used therapeutically.[170] Thiazolidinediones have been shown to alter several mediators in insulin-sensitive tissues to affect glucose and lipid metabolism, leading to a reduction in liver fat.[171] Although thiazolidinediones have been demonstrated to lower blood glucose levels in patients with type 2 diabetes,[172] some reports have reported liver damage and death from acute liver failure in patients with thiazolidinedione administration.[173,174] Troglitazone, neotroglitazone, pioglitazone, and rosiglitazone are thiazolidinedione derivatives. Troglitazone was the first thiazolidinedione approved for use in the USA in 1997.[175] However, it has been reported that troglitazone causes cytotoxicity by degrading the active protein of PPARγ.[176] Because neotroglitazone use was linked to an increased risk of liver failure, it was eventually withdrawn in the USA.[177] Nevertheless, studies show pioglitazone is effective in patients with NAFLD/NASH and that it continuously improves histological parameters and normalizes liver transaminases. However, the use of this drug has side effects such as weight gain.[178] Taking rosiglitazone for 24 weeks, also stabilized the level of LDL-C, reduced LDL-C, induced AS, and increased HDL-C level.[179] According to clinical trials evaluating liver function in individuals with type 2 diabetes, evidence shows that rosiglitazone does not cause hepatic impairment.[180] Although there are several other agonists and antagonists for PPARs, they have not been used in clinical studies.[181] Overall, it seems that thiazolidinediones derivatives are better drugs for improving liver diseases through their effects on PPARs.

Conclusion

Accumulating evidence from human and animal studies demonstrates that PPARs have multiple functions in the both health and disease that are not limited to the metabolic effects. They change the expression of numerous genes by interaction with other transcriptional factors and affect me-

tabolism, inflammation, infection, circulation, and cancer in the liver. Although there are some side effects associated with the clinical use of PPAR agents, it is hoped that more effective PPAR-based drugs with fewer side effects will be developed in the future.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study conception and design, and revision of the draft manuscript (AM), searching of the literature and drafting of the manuscript and figures (ZC), searching of the literature and drafting of the manuscript (FK). All authors made significant contributions to the study and approved the final manuscript.

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