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Emerging Role of the Peroxisome Proliferator-Activated Receptors in Hepatocellular Carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is the most common primary liver neoplasm and the third leading cause of cancer deaths worldwide. Conventional therapies are not generally effective for advanced HCC and therefore a great effort is needed in developing approaches to prevent or reverse the progression of HCC. There is an emerging body of evidence that the peroxisome proliferator-activated nuclear receptors (PPAR) regulate the growth and proliferation of HCC cells. Herein, we provide a brief introduction to PPAR biology and review recent discoveries highlighting the importance of PPAR signaling in the modulation of hepatocellular carcinoma development and growth.

Keywords: Hepatocellular carcinoma; PPARα; PPARγ; Troglitazone; Autophagy

Introduction

Hepatocellular carcinoma (HCC) is the most common malignancy of the liver and the third leading cause of cancer deaths worldwide. It is generally presented at an advanced stage, limiting patients' quality of life. The prevalence and severity of hepatocellular carcinoma is increasing worldwide and prognosis of HCC patients is still unsatisfactory due to the high rate of recurrence and metastasis. Most cases of HCC develop within an established background of chronic liver disease and therefore local treatment such as hepatic resection or radio-frequency ablation is limited to selective patients due to the high incidence of morbidity and mortality in patients with cirrhosis [1]. Since the discovery of Sorafenib, signaling pathways have become a major source of targets for novel therapies in hepatocellular carcinoma [2]. However, limited survival benefits for patients with late-stage HCC and no strong efficacy on tumor metastasis have been shown in Sorafenib-treated patients [3]. Therefore, alternative therapeutic modalities to impact HCC are needed and therefore finding of new therapeutic targets may help to develop such strategies.

The liver has a central role in governing metabolism and a plethora of signaling molecules and receptors are well-orchestrated to respond to energy status and environmental changes. One of them is the peroxisome-proliferator activated receptors (PPAR) which have revealed as a player controlling many aspects of lipid metabolism and glucose homeostasis and for this reason some of their ligands are currently used to treat diabetes type 2 and related metabolism disorders. In addition, more recent studies indicate a new and emerging role of PPARs in regulating cell proliferation and survival. Herein, we provide a brief introduction to PPAR biology and review recent discoveries highlighting the importance of PPAR signaling in the modulation of hepatocellular carcinoma development and growth.

PPAR Receptors

Nuclear hormone receptors are transcription factors activated by lipid-soluble and therefore membrane-permeable ligands, regulating the expression of target genes involved in diverse physiologic processes. They have been divided into seven different subgroups according to sequence homology and phylogenetic criteria [4,5]: NR1 (thyroid hormone like), NR2 (HNF4-like), NR3 (estrogen like), NR4 (nerve growth factor IB-like), NR5 (fushi tarazu-F1 like), NR6 (germ cell nuclear factor like), and NR0 (knirps or DAX like). These molecules are extremely important in medical research since a large number of them are implicated in diseases such as cancer, diabetes or hormone resistance syndromes.

Peroxisome proliferator-activated receptors (PPARs) belong to the first family of nuclear receptors, NR1, and present the conserved domain structures found in most nuclear receptors. It consists of an N-terminal ligand-independent activation function (AF-1) domain, a highly conserved DNA-binding domain (DBD) with two zinc fingers, a ligand-binding domain (LBD), and a second C-terminal ligand-dependent activation function (AF-2) domain [5]. The variable hinge region linking the DBD and LBD permits the structural flexibility of the receptor. DNA binding occurs through interaction by DBD with highly specific DNA regions called "response elements".

PPARs respond to specific ligands acting as a ligand-activated transcription factors regulating the expression of genes usually involved in metabolic process. In the absence of ligand, PPARs are complexed with corepressor proteins such as NCoR (nuclear receptor corepressor) or SMRT (silencing mediator of retinoid and thyroid receptors) and act as transcriptional repressors. Upon ligand binding, a conformational change is induced and the receptor heterodimerizes with the retinoid X receptor (RXR). The heterodimer then binds to the PPAR response element (PPRE) in the promoter region of the target gene, and induces the transcription of the selected gene. Activation of PPARs can also repress the transcription of targeted genes [6].

PPARs were first identified as target of small molecules causing peroxisome proliferation in liver but later, a plethora of different natural as well as synthetic ligands, including lipophilic molecules such as polyunsaturated fatty acids, prostaglandines, leukotrienes, and hypolipidemic drugs, have been described. When binding this ligands, PPARs turn these lipid signals into transcriptional changes affecting several aspects of lipid metabolism, including synthesis, transport, storage, mobilization, and oxidation, that are potentially linked to the development of some diseases such as hyperlipidemia, diabetes, and obesity. However, these receptors have also been shown to be implicated in cellular proliferation, differentiation, tumor promotion, apoptosis and immune reaction/inflammation.

Three types of PPAR have been identified known as PPARα (NR1C1), PPARβ/δ (NR1C2) and PPARγ (NR1C3) [7]. All distinct PPARs subtypes exhibit distinct patterns of tissue distribution and share a high degree of structural homology with other members of the superfamily, particularly in the DNA-binding domain and ligand-binding domain. PPARα is expressed primarily in liver and is essential for metabolic adaptation to starvation [8]. PPARβ/δ is expressed ubiquitously but recent research is focusing on his metabolic effect in skeletal muscle during endurance exercise [8]. Although PPARγ is mainly expressed in adipocytes a protective role on the development of liver diseases has become increasingly clear. Recent studies have demonstrated that the importance of PPARα and PPARγ in the regulation of cell proliferation in the liver is much higher than previously thought [9].

PPARα

PPARα is highly expressed in liver, which is closely correlated with fatty acid catabolism as a result of upregulation of the expression levels of genes involved in lipid transport, fatty acid β-oxidation, and ketogenesis. Classical endogenous PPARα ligands include unsaturated long-chain fatty acids such as palmitate, oleate, and linoleate and their thioesters (long-chain fatty acyl-CoA; LCFA-CoA) and drugs used to treat dyslipidemias. Recent findings suggest that the intermediaries of the glyceroneogenesis pathway in adipocytes, glycerate, dihydroxy acetone phosphate, glyceraldehyde-3-phosphate, and glycerol-3-phosphate bind to and activate PPARα acting as natural ligands [7].

During fasting, PPARα is activated and fatty acids derived from peripheral tissues or intrahepatic lipid droplets are catabolized in liver through β-oxidation to produce ketone bodies, which are used as fuel when glucose is scarce [10]. PPARα activation also modulates the expression of key genes involved in VLDL-TG turnover as well as apolipoproteins associated with HDL, such as ApoA-I and ApoA-II and up-regulates cellular transporters involved in the cholesterol efflux pathway [11]. Although metabolic beneficial effects of PPARα activation have been extensively described, PPARα also plays a central role in mediating transformation from hepatic steatosis to hepatocarcinogenesis and therefore the relationship between PPARα and the development of liver cancer have been the focus of considerable attention [12].

Several studies show that PPARα activation is involved in HCC development and cell proliferation in experimental animal models or in human HCC cell lines [13,14]. Activation of PPARα induces a rapid MYC activation in proliferating hepatocytes which is tightly correlated with G0/G1 to S phase transition [15,16]. Chronic administration of PPARα agonists induce tumors in mice [15] and this effect is mediated by PPARα, as inferred by the fact that PPARα-null mice fails to develop liver tumors [16]. However, transgenic mice expressing a constitutively active PPARα in hepatocytes did not develop hepatocellular carcinomas in spite of hepatocyte proliferation and hepatomegaly [13].

By contrary, treatment of HepG2 cells with clofibrate, a fibrate derivative considered as specific ligand for PPARα, caused apoptosis in a time- and concentration-dependent manner, suggesting that in some conditions PPARα ligands may inhibit HCC cell proliferation [17].

However, to the best of our knowledge, there are no studies showing the association of PPARα in human HCC carcinogenesis. Comparative studies with several species concluded that significant quantitative differences in PPARα activator-induced effects related to liver cancer formation exist between rodents and humans [18]. Nevertheless, in a preliminary study in 10 patients, the expression of PPARα was significantly higher in human hepatocellular carcinoma tissue compared with the non-cancerous sections. Moreover, the expression of PPARα-targeted genes as carnitine palmitoyltransferase 1A and cyclin D1 were also elevated in human cancerous tissue [19]. These findings indicate that PPARα activation might be associated with liver carcinogenesis and the metabolic changes accompanying the emergence of HCC.

Nonetheless, more studies are needed to establish a robust conclusion on the role of PPARα activation in HCC carcinogenesis.

PPARγ

PPARγ was cloned as a highly adipose-specific transcription factor important for adipogenic gene expression [20]. PPAR exists in two major isoforms (γ1 and γ2) which arise from four different mRNA generated by differential transcription start sites and alternative splicing of the same gene. The PPARG1, 3, and 4 mRNA isoforms are translated into the unique PPARγ1 protein whereas the PPARG2 transcript is translated into PPARγ2, containing 28 additional amino acids at its N-terminal region that increase the ligand independence of its activity [21].

PPARγ1 is expressed in all PPARγ-expressing tissues and cells and PPARγ2 is almost exclusively found in adipose tissue, where it exerts a pronounced adipogenic activity and is most likely responsible for PPARγ-mediated insulin sensitivity [22].

Natural PPARγ ligands include lipophilic compounds such as polyunsaturated fatty acids, eicosanoids emerging from the metabolism of arachadonic acid and linoleic acid, components of oxidized plasma lipoproteins, and platelet activating factor [23,24], although their physiological relevance is not always evident. Recently, nitric oxide (NO)-derived unsaturated fatty acid products like nitroalkenes have been revealed as a potent endogenous PPARγ receptor ligands [25]. In addition, a plethora of synthetic ligands, such as the thiazolidinediones (TZDs) including rosiglitazone, troglitazone, ciglitazone, pioglitazone and englitazone or novel partial agonists have been developed.

Selective PPARγ modulators bind in different manners to the ligand-binding pocket of PPARγ, leading to alternative receptor conformations, differential cofactor recruitment/displacement, differential gene expression, and ultimately differential biological responses. A classification of PPARs various ligands, chemistry and physical properties may be found in a recent review [26].

PPARγ and HCC

The important effects of PPARγ activation on HCC have been extensively demonstrated in a plethora of studies. Many current lines of evidence indicate that activation of PPARγ reduce hepatocellular carcinoma cell proliferation, migration and metastasis [27,28]. Antiproliferative effects of synthetic PPARs ligands such as troglitazone, pioglitazone, ciglitazone and rosiglitazone has been demonstrated in different HCC cell lines. These ligands inhibit the growth and proliferation of human liver cancer cells in vitro and in vivo, increase PARP and Caspase-3 cleavage and induce apoptosis [29-34]. In AML-12 hepatocytes ectopically expressing PPARγ2, troglitazone attenuated growth and inhibited expression of proliferating cell nuclear antigen (PCNA), cyclin D1, and β-catenin [30].

Moreover, the combination of rosiglitazone with the classical chemotherapeutic agent 5-fluorouracil, synergistically inhibited the proliferation of human HCC cell lines BEL-7402, HuH-7 and Hep3B [35,36]. This effect was mediated by PPARγ activation which enhanced PTEN expression and decreased COX-2 expression [36].

Accordingly, PPARγ expression in clinical samples of human HCC was significantly lower than the expression in nontumorous surrounding liver. Moreover, expression levels of PPARγ mRNA appeared related to the state of histological differentiation [33]. In line with this, activation of PPARγ with troglitazone in Hep3B and HuH-7 cells caused a dose-dependent suppression of cell viability [33]. However, a recent study about PPARγ expression in liver carcinoma showed that PPARγ was highly expressed in liver cancer tissues and in the HCC cell line Hep3B. Moreover, overexpression of the estrogen receptor in HCC cells, downregulated PPARγ and negatively regulated cellular proliferation [37]. This finding indicates that in some circumstances and depending on intracellular signaling events, activation of PPARγ may lead to increased cell growth. By contrary, studies performed by Pang et al. [27] demonstrated that β-estradiol, a well-known ligand of estrogen receptors, suppressed hepatocellular carcinoma cell invasion and activated PPARγ. Activation of PPARγ increased the expression of the plasminogen activator inhibitor-1 (PAI-1), a serine protease inhibitor which restrain degradation of extracellular matrix. In addition, overexpression of PPARγ in HCC cells elevated the level of PAI-1 and prevented cell invasion [27].

Recent findings using PPARγ knockout mice reinforce the idea that PPARγ reduces HCC carcinogenesis and acts as a tumor-suppressor gene in the liver. In a chemically-induced HCC mice model, PPARγ-deficient mice developed fewer tumors than their corresponding wild type controls [28]. In addition, when mice were treated with the PPARγ agonist rosiglitazone or the vehicle alone for 8 months, a significant reduction on the incidence of HCC was found in rosiglitazone-treated PPARγ+/+ mice, but not in PPARγ+/− mice, indicating that PPARγ suppresses hepatocellular carcinogenesis [28]. Moreover, overexpression of PPAR in the HCC cell line Hep3B, markedly suppressed HCC cell viability [28]. Authors conclude that PPARγ suppresses tumor cell growth through reducing cell proliferation and inducing cell cycle arrest and apoptosis and that loss of one PPARγ allele is sufficient to enhance susceptibility to HCC [28].

Signaling Mechanisms Involved in Ppary Antitumor Activity

The mechanisms whereby PPARγ exerts its antitumor activity are far from being clarified but several studies have shed a bit of light to the dark scenario. For instance Cheung et al. [38] performed an study to identify the molecular target of PPARγ in HCC cells and found that when cells were activated with rosiglitazone, PPARγ bound to the promoter and increased the expression of CBP/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 2 (CITED2), which was the main target of PPARγ in both normal hepatocyte cell line LO2 and HCC cell line Hep3B. Inhibition of CITED2 promoted HCC cells growth and proliferation whereas ectopic expression of CITED2 in HepG2 and BEL7404 HCC cell lines significantly suppressed cell growth and up-regulated the cyclin-dependent kinase inhibitors p15(INK4B), p21(Wat1/Cip1) and p27(Kip1) as well as several proapoptotic mediators [18]. In five different HCC cell lines, troglitazone induced cell-cycle arrest through a mechanism involving the overexpression of the cyclin-dependent kinase inhibitors p21, p27 and p18 as well as an accumulation in cyclin E [39]. Furthermore, troglitazone-promoted p27 accumulation was mediated by down regulation of Skp2, a component of the SCF ubiquitin-E3 ligase complex [40]. In serum-deprived HuH-7 cells, troglitazone caused cell cycle arrest, increased the expression of p27 and induced apoptosis through inhibition of the PI3K/Akt pathway [34]. Other signaling molecules involved in the anti-proliferative effects of PPARγ ligands in HCC cells include the hypoxia-inducible factor 1 (HIF-1)-responsive RTP801, a gen related to apoptosis under oxidative stress conditions [41] and the inhibition of the oncogenic protein Jun activation domain-binding protein 1, JAB1 [42].

Several studies have shown that cannabinoids may exert their antitumoral effects in HCC cell lines in part through PPARs activation. The synthetic cannabinoid WIN 55-212,2 (WIN) induce cell death an apoptosis in the HCC cell line BEL-7402 in a dose- and time-dependent manner [43]. Those effects as well as WIN-induced down-regulation of c-myc, were abrogated by the PPARγ antagonist GW9662 suggesting that PPARγ is involved in cannabinoid effects on BEL-7402 cells. In fact, treatment of this cell line with WIN increased the expression of PPARγ. Moreover, a cannabinoid receptor CB2 antagonist blocked this effect, indicating that CB2 may mediate WIN-induced PPARγ expression [43]. Our group recently investigated the antitumor effect of several cannabinoids on HCC cells and the involvement of PPARγ. Rosiglitazone, as well as the plant-derived cannabinoid THC and the synthetic cannabinoid JWH-015, inhibited HepG2 and HuH-7 proliferation which was abrogated by the PPARγ antagonist GW9662 [44]. The cannabinoids induced overexpression and activation of PPARγ both in vitro and in vivo. Moreover, the in vivo antitumor effect of cannabinoids in a xenograft HCC mice model depended on PPARγ activation [44].

As further research on antitumoral therapies against HCC, development of molecules which includes in one entity cannabinoid and quinone features was performed. Those cannabinoid/quinone hybrid compounds exhibited anti-proliferative properties in HepG2 with an IC50 of 30μM [45]. The PPARγ receptor antagonist GW9662, significantly prevented the cytotoxic effect of the compounds indicting that PPARγ receptor is involved in the cytotoxic effect. The fact that PPARγ receptors may be involved in the mechanism of action of the cannabinoid/quinone hybrids is not that surprising since a potent activation capacity of PPARγ by other quinone derivatives with anticancer activity has already been reported [46,47]. In the same line, emodin, a natural occurring anthra-quinone derivative and a PPARγ ligand, has antitumor effect on HCC cells [48].

HCC may originate from a subpopulation of stem-like cells, called tumor-initiating cells (TICs) or cancer stem cells. In a recent study it was shown that the PPARγ ligands 15d-PGJ2 and rosiglitazone inhibited the proliferation of HCC cancer-derived stem cells and decreased the expression of a number of stemness-related genes, including Nanog, Notch1, OCT4, and SMO, suggesting that PPARγ agonists inhibit cancer stem cell-like phenotypes [21]. In addition, PPAR agonists dramatically increased the levels of intracellular ROS in both HuH-7 and SK-Hep1 HCC cells. However, increased ROS induced hyperactivation of AKT, which significantly counteracted PPARγ agonist-mediated inhibition of stem cell-like properties. Interestingly, the combination of PPARγ ligands with an Akt inhibitor synergistically inhibited HCC cell proliferation in vitro and in vivo [21].

Intriguingly, whereas several PPARγ ligands have been shown to reduce hepatocellular carcinoma cell proliferation through PPARγ activation, PPARγ antagonists, at lower concentrations than that needed for agonists, as well as PPARγ small interfering RNAs caused HCC cell death by preventing adhesion and inducing anoikis-mediated apoptosis [49]. In fact, a reduction in the motility of HepG2 cells after they were treated with PPARγ antagonist GW9662 has also been observed [50]. In this regard, authors propose that a discrete modulation rather than complete activation or inhibition of PPARγ may be the most effective strategy for utilizing this pathway to treat HCC.

PPARγ and Autophagy

Autophagy is a lysosomal catabolic pathway by which eukaryotic cells recycle macromolecules and organelles. Materials to be degraded are engulfed by intracellular membrane vesicles named autophagosomes. Subsequently, autophagosomes fuse with lysosomes and their contents are degraded by the lysosomal acidic hydrolases [51]. Recently, this process has received much attention because when prolonged, proteins and organelles essential for basic homeostasis and cell survival are degraded, which can lead to cell death [52].

Autophagy is tightly regulated by many intracellular signals, but one of the best characterized is the pathway involving the mammalian (or mechanistic) target of rapamycin (mTOR) kinase. This kinase, which is part of two protein complexes termed mTOR complex 1 (mTORC1) and 2 (mTORC2), has a fundamental role in coordinating anabolic and catabolic processes in response to growth factors and nutrients [53]. Through the phosphorylation of several other effectors, mTORC1 promotes lipid biogenesis and metabolism and suppresses autophagy. In adipocytes, mTORC1 inhibition severely impairs adipogenesis and adipose cell maintenance by modulating the expression and the activity of PPARγ [53].

It is not yet elucidated if activation of PPARγ is concerned with autophagy. Recent reports show that in breast cancer cells, a cucurbitane-type triterpene isolated from wild bitter gourd induced autophagy acting as a PPARγ agonist [54]. This triterpene as well as troglitazone, inhibited Akt/mTOR pathway and enhanced the conversion of microtubule-associated protein 1 light chain 3 (LC3-I) into its lipidized form LC3-II, which is a hallmark of autophagy [54]. Similar results were obtained by Rovito et al. using omega-3 long chain polyunsaturated fatty acid as a PPARγ activator [55]. We have studied the involvement of PPARγ in cannabinoid-induced autophagy in HCC cells. Cannabiniod treatment of HepG2 cells as well as HuH-7 cells triggered autophagy which was prevented by the PPARγ antagonist GW9662. Furthermore, knocking down PPARγ also blocked cannabinoid-induced inhibition of cell viability and the conversion of LC3-I into LC3-II.To note, when PPARγ expression was silenced there was an increase of LC3-II and p62 not only in cannabinoids-treated cells but even in the control cells. The aforementioned results prompted us to speculate that when PPARγ is absent, autophagy is blocked after autophagosome formation and therefore LC3II increases and p62 accumulates in the autophagosome because it cannot be further degraded [44]. It is well recognized that AMPK activation promotes autophagy via mTOR inhibition. However, although cannabinoids activated AMPK and inhibited mTOR pathway in HCC cells, this was independent of PPARγ activation. Genetic inhibition of PPARγ did not have any effect on AMPK phosphorylation or Akt/mTOR/S6 axe activation in cannabinoid-treated cancer cells, suggesting that PPARγ did not play a role in those pathways. As a matter of fact, a cross-regulation between AMPK and PPARγ pathways was not seen in our studies since AMPK down-regulation by siRNA did not have any effect on PPARγ activation [44].

PPARγ and HCC migration, invasion and metastasis

In addition to the well-defined antiproliferative effects of PPARγ ligands, PPARγ exerts an inhibitory effect on the invasive and metastatic potential of HCC in vitro and in vivo. Epithelial-mesenchymal transition (EMT) is a complex process by which a polarized epithelial cell embedded in a stratified epithelium turns, via molecular reprogramming, into a fibroblastoid-like cell with enhanced migratory capacity. This confers tumor cells with abilities essential for metastasis, including migratory phenotype, invasiveness, resistance to apoptosis, evading immune surveillance, and tumor stem cell traits. One of the best characterized phenotypic changes associated with EMT is the diminished expression of E-cadherin, a cell anchoring protein, which causes the disruption of tight epithelial cell-cell contacts and the release of invasive tumor cells from the primary tumor [56]. Recent research shows that activation of PPARγ by rosiglitazone and troglitazone significantly increased E-cadherin expression and reduced the motility and migration of HepG2 cells [50]. In addition, ectopic expression of PPARγ by Ad-PPAR or activation by its agonist rosiglitazone, in two HCC cell lines (MHCC97L, BEL-7404) inhibited metastatic activity in vitro, and reduced the incidence and severity of lung metastasis in an orthotopic HCC mouse model [57]. PPARγ reduced wound healing, cell migration, and invasion through downregulation of metalloproteinases 9 and 13 and increased expression of TIMP3 and E-cadherin. Moreover, the combination of Ad-PPARγ and rosiglitazone resulted in an enhanced anti-metastatic effect [57]. In HepG2 cells, activation of PPARγ with GW1929 inhibited cell invasion. Furthermore, knockdown of PPARγin this cells avoid the inhibition of cell invasion in response to GW1929. On the contrary, overexpression of PPARγ in HCC cells elevated the level of PAI-1 and inhibited cell invasion [27].

These findings implicate that PPARγ regulates cell adhesion and therefore is a target for the treatment and prevention of HCC cell invasion and metastasis.

Other PPARγ effects

HCC often develops in the context of abnormal hepatocyte growth associated with previous liver disorders such as cirrhosis, fibrosis and alcoholic or nonalcoholic steatohepatitis. Liver injury originates excessive production of the key profibrotic cytokine transforming growth factor-β (TGF-β), which contributes to the instauration of pathological fibrosis promoting the activation and proliferation of hepatic stellate cells, which in turn increase the synthesis of extracellular matrix proteins, causing a gradual destruction of normal tissue architecture and function. Increasing evidence supports the notion that PPARγ suppress the TGF-β pro-fibrotic activity via inhibition of its signaling cascade [58]. In a recent study by Pawella et al. [59] activation of PPARγ induced the expression of the lipid droplets-associated proteins perilipin and adipophilin which play an important role in hormone-dependent lipolysis in the liver.

This may indicate that PPARγ regulates different stages of liver disease and therefore, modulation of PPARγ activity could be useful to treat and prevent not only hepatocarcinogenesis but previous liver diseases.

Conclusions

PPAR receptors are key factors modulating not only liver cells metabolism but also growth and proliferation. Whereas PPARα is involved in hepatocarcinogenesis and the progression from hepatic steatosis to hepatocarcinogenesis, PPARγ regulates the opposite. Several recent studies have demonstrated that activation of PPARγ can suppress growth in proliferating HCC cells as well as invasion, migration and metastasis. A number of studies have also been performed to confirm the potential in vivo anticancer effects of PPARγ ligands.

Therefore modulating PPAR signaling pathways represents a potential novel strategy for inhibiting HCC carcinogenesis and its progression. However further investigations are needed to explore new combinational chemotherapies that impact PPARs. This will provide new alternative anti-tumor treatment opportunities.

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