Hepatic PPARs: Their Role in Liver Physiology, Fibrosis and Treatment

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Abstract: Complex molecular and cellular mechanisms are involved in the pathway of liver fibrosis. Activation and transformation of hepatic stellate cells (HSCs) are considered the two main reasons for the cause and development of liver fibrosis. The peroxisome proliferator-activated receptors (PPARs) belonging to the family of ligand-activated transcription factors play a key role in liver homeostasis, regulating adipogenesis and inhibiting fibrogenesis in HSCs. Normal transcriptional function of PPARs contributes to maintain HSCs in quiescent phase. A reduced expression of PPARs in HSCs greatly induces a progression of liver fibrosis and an increased production of collagen. Here, we discuss role and function of PPARs and we take into consideration molecular factors able to reduce PPARs activity in HSCs. Finally, although further validations are needed, we illustrate novel strategies available from in vitro and animal studies on how some PPARs-agonists have been proved effective as antifibrotic substances in liver disease.

Keywords: Cytokines, genes, HSCs, ligands, liver fibrosis, microcirculation, PPARs, antifbrotic therapy, transcription factors.

1. INTRODUCTION

Molecular and gene studies have opened new points of view on the pathogenesis of liver fibrosis clarifying some of the most important pathophysiologic mechanisms, among which very important is the one involving the role of peroxisome proliferator-activated receptors (PPARs) in hepatic stellate cells (HSCs) (Fig. 1).

PPARs, belonging to the nuclear hormone receptor superfamily, are transcription factors that bind DNA and regulate transcription in a ligand-dependent manner. They regulate gene expression after binding with RXR (Retinoid X Receptor) as a heterodimeric partner to specific DNA sequence elements termed PPRE (peroxisome proliferator response element [1].

Three main isotypes of PPARs, PPAR□ (also called NR1C1), PPAR□and □(PPAR □/ □) that are the same receptor (also called NUC1 or FAAR), and PPAR□ (also called NR1C3), are known: each one of them has a distinct, tissue-specific pattern of expression [2].

PPARs control the transcription of several genes involved in fatty acid oxidation and cell differentiation and regulate several biological processes such as development, differentiation, neoplastic conversion, inflammation and wound healing [3].

In the liver, PPARs have important functions: they contribute to maintain HSCs in a quiescent condition; indeed, PPAR□ is able to inhibit type I collagen expression at the level of transcription [4]. HSCs, that are pleiotropic cells strictly located next to hepatocyte laminates in the perisinusoidal space of Disse, whether activated or transformed, greatly favour the development of liver fibrosis [5] (Fig. 2).

In HSCs, equilibrium between adipogenic and myogenic genes is also regulated by epigenetic modifications. Despite the mechanism is largely unknown yet, DNA methylation in CpG islands of the gene promoter regions seems very important. Several studies demonstrated an increased hypermethylation rate of promoter in cirrhotic patients compared to normal controls [6, 7].

Depletion of microRNA132 (miR132) leads to overexpression of methyl-CpG binding protein 2 (MeCP2), that normally is suppressed. MeCP2 induces generation of enhancer of zeste homolog 2 (EZH2) and hypermethylation of lysine 27 histone 3 (H3K27). Alternatively, MeCP can directly bind CG island and promote methylation of H3K9. Methylated H3K9 can recruit transcriptional suppressor HP1□and bind to the promoter, exon1, exon2 and 5' end of PPAR□ All these mechanisms conduct to a suppression of PPAR□[8, 9].

Another pathway shows a key role of necdin: this protein, normally expressed in neurons, skeletal and smooth muscle cells, can prevent HSCs from developing adipogenic characters. In fact, Necdin combines with GN box of promoter of wingless-related MMTV integration site 10b (Wnt10b). Promotion of Wnt10b expression leads to the generation of EZH2 and hypermethylation H3K27 [10].

Also MeCP2 enhances the expression of a methyltransferase of H3K4 promoter called ASH1 that leads to recruitment of □SMA, collagen I, TIMP-1 and TGF□1 genes [11].

MeCP2 is also partially involved in epigenetic regulation of expression of inflammation chemokine [12].

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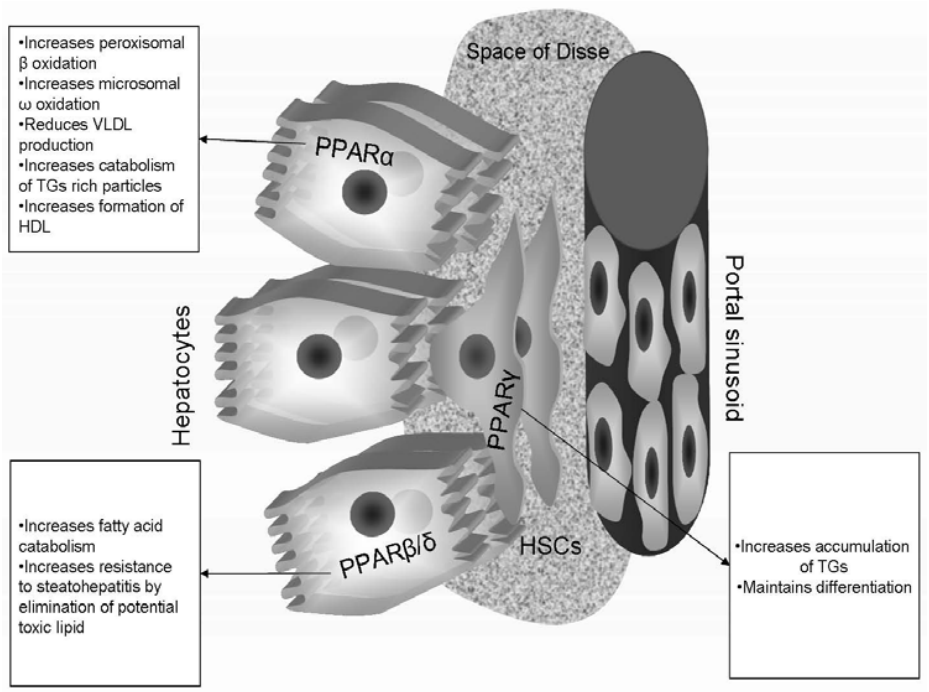


Fig. (1). Schematic view of the portal microcirculation under physiological conditions of the liver: you can see the portal sinusoid with, around, space of Disse, hepatic stellate cells (HSCs) and hepatocytes. PPAR□inside HSCs and PPAR□and PPAR□□inside hepatocytes are respectively involved in favouring the maintainance of normal liver function and metabolism.

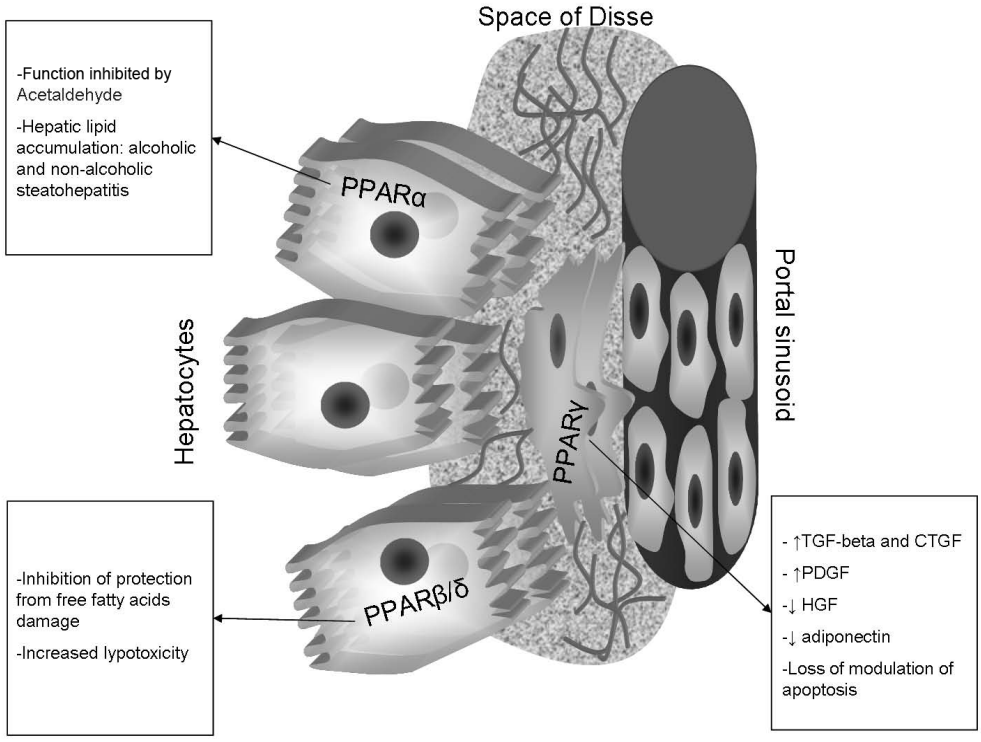


Fig. (2). Schematic view of the portal microcirculation in liver fibrosis: portal sinusoid with increased amount of collagen type 1 in space of Disse, activated hepatic stellate cells (HSCs) and hepatocytes are represented. PPAR□inside HSCs and PPAR□and PPAR□□inside hepatocytes are respectively altered and liver function is dysregulated.

Another epigenetic mechanism involves metalloproteases: an impaired histone deacylation during HSC differentiation may lead to accumulation of histone deacetylase-4, which can suppress the activity of MMP gene promoter in

quiescent HSCs, determining accumulation of extracellular matrix [13].

The telomere length may play an important role. Previous studies demonstrate that hypermetilation of DNA is correlated with an increased activity of telomerase [1]. This epigenetic mechanism seems to be involved in transgenerational inheritance: in 2009, it was demonstrated that offspring of murine models exposed to CCL4 injury developed tolerance to liver damage and a lower degree of fibrosis [14].

Epigenetic mechanisms, although largely unknown, seem to be a very intriguing area of research for the next years.

Before HSCs transform themselves into myofibroblasts, a number of stimuli (viral, ROS, endotoxins, alcool, etc) act on several cellular types in the liver (Kupffer cells, macrophages, neutrophils, T cells, natural killer and natural killer T cells) [15]; these cells secrete specific cytokines to favour initiation and progression of hepatic fibrosis by means of a reduction of activity of PPARs in HSCs. Indeed, TNF-□ mediated inhibition of PPAR□ transactivity may result in increased HSCs activation and proliferation [16, 17].

It is known that the activity of PPARs depends on ligand-induced conformational changes, a mandatory process for a correct functioning of ligand-regulated nuclear receptors [18]. Conformational changes of PPARs facilitate their dissociation from corepressor molecules and their interaction with multisubunit coactivators.

Therefore, lack of dynamic and coordinated changes in PPARs expression and also perturbations in the expression of coactivators may alter the correct function of PPARs and favour a change of phenotype from quiescent to activated in HSCs.

Inhibition of fibrosis is one of the most attractive biological process, object of several studies [19]. Here we want to review the complex molecular mechanisms and the signaling involved in the cross-talk among coactivators, corepressors and PPARs in HSCs.

We also summarize some of the several strategies based on PPAR□ stimulation that have proven to be potential antifibrotic approaches.

2. PPARS IN LIVER PHYSIOLOGY

2.1. Structure of PPARs

PPARs share a similar modular structure: A/B domain (ligand- independent activation domain), C domain (DNA binding domain), D domain (hinge domain), and E/F domain (ligand-binding domain – LBD) [20]. The chief fragment of the N-terminal domain A/B is an □-helix fragment possessing a ligand-independent activating function (AF-1) [21]. In A/B domain there is a residue of serine in position 112, subject to phosphorylation by mitogen-activated protein kinase (MAPK) pathway, resulting in failure to intramolecular communication between the domains, and reduction in ligand-binding affinity. C domain contains two zinc fingers, each encoded by two different exons (2 and 3) which, together with particular aminoacid sequences, binds DNA. C domain also takes part in dimerization with RXR. D domain is a flexible hinge between C and E / F domains [22]. It acts as a binding cofactor and contains a specific amino acid sequence recognized by the transport proteins, which allows the movement of the protein synthesized, from the cytoplasm to the nucleus. The largest domain is the LBD (E/F domain) located at the C-terminus [23]. The LBD contains a fragment called ligand-dependent activation function 2 (AF-2), engaged in the recruitment of PPAR□ cofactors to assist the gene transcription processes [24].

The unliganded LBD possesses a small □-sheet of four strands and 12 □-helices that are folded into three layers to create a central hydrophobic ligand-binding pocket. AF-2 is in helix 12, located between □-strand and helix 3, that closes the ligand binding site in response to a ligand, resulting in a transcriptionally active form of the receptor [25].

Despite this similar structure, the difference between PPARs can be linked to ligand specificity. In this regard, PPAR□ cavity is narrower in the region adjacent to the AF-2 helix and this may explain why large headed TDZs and L-tyrosine based agonists show little or no ability to bind PPAR□ [26].

The difference between PPAR□ and PPAR□ may be explained by the interaction with Farglitazar and GW409544: in fact, Farglitazar, shows higher PPAR□ selectivity compared to that of GW409544, due to the presence of three additional atoms located near the carboxylate head group. Due to the presence of Tyr314 in PPAR□ compared to the correspondent His 323 in PPAR□ farglitazar shows stearical clash in interaction with PPAR□ [26].

Regarding LBD, a “mouse trap model” was proposed [27] whereby a ligand-induced conformational transition permitted the reposition of the amphipathic alpha-helix of the AF-2 activating domain and, forming the active form of the receptor that can bind a co-activator.

This is crucial in the interaction with the agonist GW1929, a pan-agonist that stabilizes H11 and H12, in contrast with the partial agonist nTZDpa and the antagonist GW9662 [28]. Furthermore PPAR□ and PPAR□ show that H12 is very dynamic even in the absence of ligand, and can adopt the active form spontaneously [29], in agreement with the existence of a basal activity in the absence of ligand [30]. These conformational changes, that can ensure a constitutive activity of PPARs, depend on highly conserved residues among the three isotypes [31, 32].

Allosteric alterations are also important in regulation of PPARs with coactivators and corepressors, that stabilize the molecule in an active and, respectively, inactive form. The nuclear receptor interaction domain of the co-activators contains LXXLL motif that forms two turns of □-helix and binds into a hydrophobic cleft on the surface of the receptor. The latter is formed upon stabilization of active conformation of AF-2 in H12 [33].

Corepressor motif instead is LXXXIXXXL, that repositions the AF-2 helix and prevents it from going back to active positions [34].

2.2. PPAR □ in Hepatocytes

Peroxisome proliferator-activated alpha, also known as PPAR□, NR1C1; hPPAR; MGC2237; MGC2452, is a nu-

clear-hormone transcription receptor of 468 amino acids coding by 22q13.31 [35]. 14 polymorphisms are known, at least (Table 1) [36].

Table 1. PPAR□Polymorphisms

P22R
V227A (rs1800234)
A268V (rs1042311)
D140Y
D304N (rs1800242)
R127Q (rs1800204)
G395A (rs2229245)
R131Q
D409T (rs1800243)
L162V (rs1800206)
R178G
Q413L (rs9615759)
D140N
G395E

The expression of the PPAR□ gene is regulated by the hepatocyte nuclear factor-4 (HNF4), that enhances hPPAR □ promoter activity. In contrast, the nuclear receptor COUP-TFII down-regulates the hPPAR □promoter activity. PPAR□ binds the □HNF4-RE, leading to its expression in hepatocytes [37] that is regulated by the ubiquitin proteasomal degradation system [38].

PPAR□is regulated also by repressive post-trascriptional mechanisms such as

- PPAR□2, a A truncated isoform resulting from a post-translational exon skipping [39]

- post-translational modifications such as phosphorylation, [40-42].

PPAR□, like many non-steroid members of the nuclear receptor (NR) family, functions as an obligate heterodimer with another nuclear receptor, retinoid X receptor (RXR; NR2B) [43]. The PPAR□/RXR heterodimers can form independently of the PPAR□ ligand and these unliganded heterodimers recruit corepressor protein complex and inhibit target genes transcription [44]. Upon ligand binding, the corepressor complex is released from the PPAR□/RXR heterodimer, and the coactivator complexes will be recruited to the promoter region of target genes to initiate transcription [5]. The PPAR□/RXR heterodimers bind to a specific DNA sequence element called peroxisome proliferator response element (PPRE) [45].

RXR is also partner of other NRs; a possible competition mechanism between NRs for this common binding partner may exist [46]. Transcriptional activation of genes is a complex process, which involves the participation of several transcription coregulators. PPAR□, interacting with coactivators or corepressors, augments or represses, respectively, its activity [47] (Table 2) [36].

The binding of ligand to a nuclear receptor favors

- the release of corepressors through the recruitment of coactivator complexes, such as members of the SRC-1/p160 family, which exhibit histone acetyltransferase activity required to facilitate chromatin remodeling.
- the docking of other coregulators, either singly or as preassembled multisubunit protein complexes, including mediator complex (MED),
- the interaction of ligand-activated receptor with RNA polymerase
- the transcription of a specific set of genes [48]

All PPARs participate in energy metabolism: PPAR□and PPAR□/□act as catabolic regulators of energy expenditure, while PPAR□ regulates anabolic metabolism [49]. Hepatic lipid metabolism principally involves three aspects: lipogenesis, oxidation of fatty acids and secretion of lipids.

Emerging evidence suggests that PPAR□ also influences lipogenesis by increasing the transcription of Scd-1 and other lipogenic genes by regulating the primary transcription factors liver X receptor □(LXR□).

This function is regulated by the LXRs ligand activation that represses PPAR□ signaling through reduction of stimulated-PPAR□/RXR binding to PPRE, as observed in primary culture of hepatocytes and mouse liver [50, 51]. Another transcription factor, regulator of the hepatic lipogenesis, and inhibitor of PPAR□ is SREBP-1c [52].

The involvement of PPAR□in lipogenesis may suggest a fail-safe compensatory mechanism for the removal of important fatty acids, for example, during starvation [53].

Table 2. Corepressor and Coactivators of PPAR□

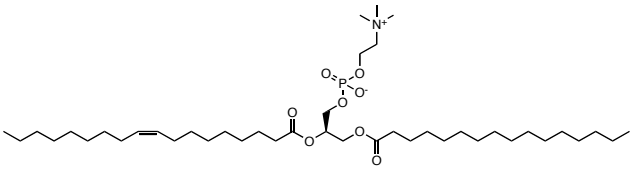
PPAR□Corepressor	PPAR□Coactivators
N-CoR (nuclear corepressor) SMRT (silencing mediator for retinoid and thyroid hormone receptors) Receptor Interacting Protein 140 (RIP140)	SRC-1 (steroid receptor coactivator-1) CBP/p300 SRC/p160 family PBP/MED1 (PPAR-binding protein/TRAP220/DRIP205/ mediator subunit 1) PRIP/NCoA6 (ASC2/RAP250/TRBP/NRC) PRIC285 PRIC295 PRIC320 PGC-1□ PGC-1□ as well as coactivator-associated proteins PIMT (NCoA6IP) and CARM-1

PPAR□ regulates fatty acid oxidation in the hepatocytes acting on genes of the classical inducible peroxisomal (□-oxidation and microsomal □-oxidation) and key enzymes (Table 3) [54].

Dicarboxylic acids are unique because they serve as substrates for the peroxisomal □-oxidation system and also as ligands for PPAR□, streamlining their own metabolism by inducing PPAR□ activation and thus regulating all three fatty acid oxidation enzyme pathway.

PPAR□ may be activated by several endogenous molecules, such as satured and unsatured long chain fatty acyl-CoA and unsatured long chain fatty acids, through ligand-induced conformational changes (large molar ellipticity changes) [55].

The most studied endogenous PPAR□ ligand is the 1-palmitoyl-2-oleoyl-sn-glycerol-3-phosphocholine16:0/18:1-GPC (1); it has been demonstrated to be able to induce PPAR□-dependent gene expression and to decrease hepatic steatosis when fatty acid synthase enzyme activity is present [56, 57]. Another endogenous molecolar factor able to reduce hepatic fat accumulation is adiponectin, an adipocyte produced peptide hormone that, by means of activation of PPAR□, induces hepatic fatty acid oxidation [58].



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PPAR□ ligands reduce very low density lipoprotein (VLDL) production and enhance the catabolism of triglycerides (TG)-rich particles and this indirectly decreases small dense LDL (sdLDL) particles [59, 60], enhancing the formation of high density lipoprotein (HDL) particles and hepatic elimination of excess cholesterol. The activity of ApoC-III, which is an inhibitor of both lipoprotein lipase (LPL) activity and remnant clearance, is lowered by PPAR□ agonists. HDL apolipoprotein genes apoA-I and apoA-II are activated by PPAR□ by direct transcriptional control [61]. Thus, PPAR□ activation by fibrates and other compounds, elicits a global normolipidemic response, by reducing TG-rich particle production, increasing their lipolysis, and promoting HDL metabolism. PPAR□ also shows an important role in reducing inflammation. In fact, Leukotriene B4 (LTB4) is a PPAR□ agonist and a powerful chemotactic inflammatory eicosanoid. Stimulation of PPAR□ by LTB4 causes expression of genes of the □- and □-oxidation pathways that neutralize and degrade LTB4 itself [62].

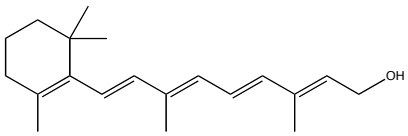
2.3. PPAR □/□ in Hepatocytes

PPAR□/□, also known as FAAR, NUC1, NUCI, NR1C2, NUCII, PPAR□, PPAR□, is coded by chromosome 6p21.2 and exists in at least 3 isoforms: 401, 361 and 402 amino acids generated by alternative splicing. [63]. An interesting study demonstrated that PPAR□/□ has a molecular structure very similar to that of PPAR□ [64]. PPAR□/□ as other PPARs, forms an obligate heterodimer with RXR and binds to specific PPRE found on target genes [65]. Post-transcriptional modifications include phosphorylation, ubiquitinylation, and sumoylation [47]. PPAR□/□ expression is induced by protein kinase C (PKC) activation [66] which plays an important role in inflammation. After post-transcriptional modifications, PPAR□/□ activates or represses target genes depending on cellular expression pattern of co-activators and co-repressors [67].

PPAR□/□, unlike PPAR□ and PPAR□ that are localized mostly in the liver and adipose tissue, is ubiquitous, but has a higher expression in intestine, keratinocytes and liver [68].

PPAR□/□ is expressed in quiescent HSCs, and especially in activated HSCs in vitro and in vivo but its role is not completely clear yet; indeed PPAR□/□ favors HSCs proliferation but also counterbalances this effect expressing genes involved in esterification of vitamin A (2) and downregulating proinflammatory gene expression, thus working to maintain HSCs in a quiescent phase [69-71].

Liver function of PPAR□/□ has been object of an interesting study demonstrating that adenovirus-mediated liver-restricted PPAR□/□ activation reduces fasting glucose levels in high fat- and in chow-fed mice with concomitant increase in accumulation of glycogen [72].



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Studies on PPAR□/□ –/– mice have better clarified the principal function of this transcription receptor factor [73]. During normal diet, PPAR□/□ –/– mice have elevated plasma triglycerides and free fatty acids, but normal values in either total cholesterol or phospholipids [74]. After a 10 weeks high fat diet, in comparison with wild-type controls, PPAR□/□ –/– mice have elevated serum values of triglyc-

Table 3. Genes and Protein Expressed by Activated PPAR□

Enzymes regulated by PPAR□	Genes regulated by PPAR□
Long chain acyl-CoA synthetases carnitine palmitoyl transferase 1,2-enoyl-CoA hydratase 3-hydroxyacyl-CoA dehydrogenase 3-keto acyl-CoA thiolase	acyl-CoA oxidase 1, ACOX1 hydratase-dehydrogenase multifunctional/bifunctional enzymes MFP1/L-PBE Pancreatic Trygliceride Lipase PTL

erides, an increased rate production of hepatic VLDL and lowered LPL [75]. According to these authors, PPAR□□ plays a key role in regulating levels of serum triglycerides in high fat fed mice, by modulating both VLDL production and LPL-mediated catabolism of VLDL-triglycerides; this suggests a potential therapeutic role for PPAR□/□ in improving serum lipids of patients with metabolic syndrome [75].

PPAR□/□ also up-regulates the fatty acid synthesis program as well as the lipogenic transcription factor and co-activator, SREBP-1c and PGC-1□[72]. In the same study, an increased resistance to steatohepatitis was demonstrated. These data suggest a role of PPAR□/□ in the elimination of potentially toxic lipid through the accumulation of TG or their transformation into less toxic lipids. Paradoxically, a link between PPAR□/□ and AMP-activated protein kinase (AMPK) determines suppression of lipogenesis and glycogen synthesis [76]. Interestingly, adPPAR□/□ livers have increased expression of adiponectin receptor 2: therefore, a further activation of AMPK may be due to adiponectin [72].

PPAR□/□ cells also contribute to lower the level of pro-inflammatory molecules functioning as a nuclear sensor of dietary fats capable of modulating the immune response through regulation of metabolic programs [72, 77].

Finally, it has been shown that PPAR□/□ has hepatoprotective effects being able to modulate NF-kB signaling thus attenuating carbon tetrachloride hepatotoxicity [78].

Also it has been shown that agonists for all three PPARs (GW7647 for PPAR□, GW0742 for PPAR□, and BRL49653 (rosiglitazone) for PPAR□) decrease leptin and interleukin-6 secretion whereas PPAR□ and PPAR□/□ agonists increase hepatocyte growth factor secretion [79]. Therefore adipocytes are stimulated to produce IL 13 and 4, which in turn allows the macrophage PPAR□/□ overexpression [80]. Thus, there is a decrease in inflammation which is connected to increased insulin sensitivity of adipose tissue.

2.4. PPAR□ in Hepatic Stellate Cells

Peroxisome proliferator-activated □ also known as GLM1, CIMT1, NR1C3, PPAR□ is a human hormone receptor coded by chromosome 3p25 [81]; it includes 9 exons designated as follow: A1, A2, B, and 1–6. In humans, four different subtypes of PPAR□mRNA (□1, □2, □3, and □4) transcribed from four different promoters were found. [82-84]. PPAR□1 predominates quantitatively. mRNA PPAR□1 shows the highest expression levels in adipose tissue and in the large intestine, while it is barely detectable in the skeletal muscle [82]. hPPAR□2 and □4 mRNA appear to be limited to the adipose tissue [84], while hPPAR□3 mRNA is expressed in the large intestine, white adipose tissue (WAT) and macrophages [83]. Both promoter regions of mPPAR□1 mPPAR□2 show consensus sequence-binding transcription factors such as CCAAT / enhancer binding protein (C / EBP), hepatocyte nuclear factor 5 and 3 (HNF5 and HNF3), and adipocyte determination and differentiation factor 1/sterol response element binding protein 1 (ADD-1/SREBP-1). However, unlike mPPAR□2, mPPAR□1 contains a large block (of Approximately 550 bp) of a (C + G)-rich sequence, suggesting the possibility of a methylation, resulting in inhibition of the expression of the gene [85].

Despite four distinct mRNA subtypes, PPAR□exists in two protein isoforms (designated hPPAR□1 and □2) resulting from alternative promoter usage and alternative splicing at the 5' end of the gene. hPPAR□1, □3, and - □4 mRNA give rise to an identical protein product, hPPAR□1 (477 aa). PPAR□1 is coded by exons A1,A2,1-6; PPAR□3 is coded by exons A2,1-6 and PPAR □4 is coded only by exons 1-6. hPPAR□2 mRNA encodes the hPPAR□2 protein with 30 extra N-terminal amino acids (505 aa) encoded by the B exon [85].

PPAR□is a nuclear receptor factor whose principal function is to regulate the sinthesis of fibrogenic molecules such as TGF-□, □-SMA, suppressing expression of their genes; PPAR□has interactions with insulin pathway in HSCs impeding the development of insulin resistance, maintains normal plasma free fatty acids level, regulates cell growth and cell differentiation and thus helps control chemotaxis, prevent the induction of fibrosis and reduce the progression of preexisting fibrosis [4, 34].

Adiponectin seems to be the most important effector for PPAR□antifibrotic hepatic action [86].

PPAR□plays an important role in adipogenesis. First of all, PPAR□induces production of several specific adipose marker such as adipocyte fatty acid binding protein (aP2) [26], phosphoenolpyruvate carboxykinase (PEPCK) [27], and LPL [61]. PPAR□favours the differentiation and production of small adipocytes, that are more insulin-sensitive than large adipocytes; PPAR□also induces apoptosis of large adipocytes. This effect on differentiation of adipocytes is favoured by TZD class drugs [28].

In adipogenesis, PPAR□shows a positive feedback with C/EBP transcription factors (C/EBP-□, -□, and □): C/EBP □ and □are activated in response to insulin or glucocorticoids in the initial stage of adipogenesis and induce production of PPAR□ In the final stage of this process PPAR□stimulates production of C/EBP□that, in turn, acts on the expression of PPAR□ gene, binding the same DNA sites induced by C/EBP-□ and □ [29, 30]. This positive feedback can be blocked by TNF □with a lipid depletion and a complete reversal of adipocyte differentiation [31]. In addition, TNF □ suppresses several adipocyte genes, such as those encoding aP2, adipsin, and insulin-responsive glucose transporter (GLUT4) [32]. Leptin also controls this process, with the induction of lipolysis and glucose utilization in adipocytes, with a functional antagonism between C/EBP□ and PPAR□ [33]. In addition, the transcriptional factor ADD1/SREBP1 modulates PPAR□ activity, through the production of endogenous ligands for PPAR□[32].

The pivotal role of PPAR□ in adipogenesis and lipid regulations is demonstrated also by the partial lipodystrophy in patients with several missense mutation in PPAR□[34]. Moreover, ectopic expression of PPAR□ promotes adipogenesis in nonadipogenic fibroblastic cells such as NIH-3T3 cells [87].

PPAR□plays an important role in insulin sensitivity as demonstrated by a polymorphism of PPAR□ 2, called Pro12A1a, that is associated with lower BMI and enhanced insulin sensitivity [88]. In mouse model in vivo, S112A mutation preventing phosphorylation in Ser-112 of PPAR□im-

peded obesity-associated to insulin resistance [89]. Studies in liver PPAR□knockout mice with adipose tissue, showed that they developed relative fat intolerance, increased adiposity, hyperlipidemia, and insulin resistance; PPAR□ exhibits an impaired plasma uptake of TGs and TG deposition in muscle and adipose tissue, that contributes to insulin resistance [90]. Thus hepatic PPAR□contributes to TG homeostasis, regulating both TG clearance and lipogenesis.

The similarities between HSCs and adipocytes are deduced from several circumstances: HSCs express adipocyte-specific genes such as leptin [91], adiponectin [92], resistin [93] and adipsin [94] and have the capacity to accumulate triglycerides as well as adipocytes [95]. Quiescent HSCs express type IV collagen similarly to adipocytes, whereas the activated HSCs express collagen type I and III as well as fibroblasts preadipocytes [9]. Cytokines and growth factors which block the differentiation of adipocytes (Epidermal growth factor/TGF alfa, TGF beta, TNF alfa, IL-1, monocyte chemotactic protein 1 [MCP-CCL2]) activate also the HSCs, suppressing the expression of adipogenic transcription factors (CCAAT/enhancer binding protein [C-EBP □, □and □, sterol, regulatory elementi binding protein-1c [SREBP-1c], LXR □, PPAR □ etc.) [96].

PPAR □is the most important regulator of adipocytes differentiation and the central element in the process of activation and transdifferentiation of HSCs. PPAR□ activated by ligand plays an important role in reducing and preventing liver fibrosis [97].

Recently, it has been demonstrated that the adenovirus-mediated expression of PPAR□in activated HSCs determines the suppression of production of type I collagen, □ smooth muscle actin and TGF □1 (typical of activated HSC) and the restoration of the ability of HSCs to accumulate retinyl palmitate, unique and specific function of quiescent HSCs in vivo [98]. This method allowed to avoid the use of agonists that may have receptor-independent effects.

The similarity between adipocyte and HSCs, due to the common mesenchymal origin, is not total: HSCs in fact express PPAR □1, whereas adipocytes express PPAR □2 [4].

3. PPARs IN LIVER FIBROSIS

3.1. PPAR □ in Hepatocytes

In neither rodents nor in human HSCs, PPAR□ mRNA is found [99]. However, quite recently, the pivotal role of PPAR□ in alcoholic liver disease was highlighted [100].

In cultured hepatoma cells, ethanol inhibits PPAR□ transcriptional activity to bind its PPRE consensus sequences [50]. This inhibitory effect was confirmed in vivo on ethanol fed Sv/129 mice and rats [50].

Acetaldehyde, a hepatotoxic molecule, is produced by ethanol oxidation mediated by alcohol dehydrogenase [101, 102]; this metabolite inhibits PPAR□ activation of receptor genes and prevents PPAR□ and PPAR□ retinoid X receptor (RXR) from interacting with DNA [103, 104].

Acetaldehyde, and more generally ethanol metabolism, slows down the response of hepatocytes to free fatty acids mediated by PPAR□ [100]. PPAR□ promotes the expression of catalase and Cu2+,Zn2+ - superoxide dismutase (SOD1), that play an anti-oxidative role [105, 106]; in presence of acethaldeyde, PPAR□ is hampered in performing its anti-oxidative function and oxidative stress increases.

In patients with alcohol liver diseases, an increased plasma level of endotoxin was detected [107-111] compared to healthy people and non-alcoholic cirrhotic patients; TNF□ and TNF□ soluble receptors have been shown to correlate with the degree of endotoxemia and liver disease stage in patients with alcoholic liver disease [107]. These findings may be motivated in chronic ethanol users by an increased intestinal permeability that persisted after two weeks of sobriety [112, 113].

In alcoholic liver disease, inflammation response plays a pathophysiological role, involving TNF□, NF-kappaB, adiponectin, LPS, Kupffer cells, HSCs and PPAR□. In 2004, a relationship was demonstrated between the tumor necrosis factor/nuclear factor-kappaB (TNF/NF-kappaB) pathway and PPAR□ in PPAR□ knockout mice that were fed with a diet containing 4% ethanol for six months; mice showed hepatomegaly, hepatic phlogosis, cell toxicity, fibrosis, increase of apoptosis and mitochondrial swelling and changes in ethanol and acethaldehyde metabolism, oxidative stress, inflammation, hepatocyte proliferation, fibrosis and mitochondrial permeability transition activation [114]. These findings may be explained by two molecular mechanisms of PPAR□: transactivation and transrepression [115, 116]. Transactivation of PPAR□ requires a direct inhibitory interaction with p65, one of two components of NF-kappaB, on NF-kappaB transcription with the induction of a co-activator [100]. Transrepression of PPAR□ involves an indirect inhibition of NF-kappaB transcription through induction of 1-kappaBalpha, which binds NF-kappaB, preventing its translocation into the nucleus.

An increase in plasma endotoxin and endotoxin-induced cytokines, as TNF□, IL1, IL2, IL6 and IL8, was hypothesized to have an important role also in pathophysiology of steatohepatitis [100].

Indeed, in animal models, the dysfunction of PPAR□ is implicated in the pathogenesis of steatohepatitis [117]; the ensuing suspicion that the dysfunction of PPAR□ may contribute to alcoholic and non-alcoholic steatohepatitis is also great in humans since its dysfunction is associated with hepatic lipid accumulation [118, 119].

Hepatocyte damage, inflammation and fibrosis are the key factors that promote the progression from simple steatosis to steatohepatitis [176]. Activated HSCs significantly contribute to cytokine expression during steatohepatitis. Fat accumulation in the liver induces hepatic cell cytotoxicity either directly or through sensitization of other agents that, together with the increased cytokine production and reactive nitrogen species, contribute to imbalance mithocondrial function [176]. Mithocondrial dysfunction favours fatty acid oxidation and generation of reactive oxigen species. Moreover, the HCV core protein down-regulates the expression of PPAR□ and steatosis may also result as a direct consequence of viral protein infection in HCV genotype 3 infection [120, 121].

All of this causes hepatocyte damage, oxidative stress, inflammation, endoplasmic reticulum stress and insulin resistance whose direct effect is to cause an elevated insulin signaling that stimulates HSCs activation by inducing mitogenesis and collagen synthesis [122]. The final outcome, through the passage to HSCs activation and transformation, is liver fibrosis [123].

PPAR□ demonstrates an anti-inflammatory role during the course of cytokine-induced phlogosis; but since acetaldehyde inhibits the physiological function of PPAR□, chronic ethanol use impairs the anti-inflammatory role of PPAR□ [114, 124, 125].

Adiponectin is an adipokine produced by adipocytes and fat tissues [126, 127]. Decreased levels of adiponectin are associated with obesity [128], type II diabetes [129, 130], atherosclerosis [131], inflammation [128] and animal models of alcoholic and non-alcoholic liver disease [132, 133]. In 2003, it was demonstrated that chronic assumption of an high-fat, ethanol-containing diet reduced adiponectin serum levels by 30-40% after three to four weeks; the decrease of adiponectin correlated with the development of liver damage in mice [132]. Indeed, adiponectin activates PPAR□ and impairs sterol regulatory element binding protein-1 (SREBP-1); therefore, in alcoholic liver disease, adiponectin may play its hepatic protective role regulating trascriptional factors that, in turn, control fatty acid synthesis [134-136] by means of PPAR□.

3.2. PPAR□/□ in Hepatocytes

PPAR□/□ has a pivotal role in metabolic homeostasis and disorders. The reported effects of PPAR□/□ ligands include: correction of dyslipidemia and hyperglycemia, prevention of diet-induced obesity, increase of insulin sensitivity and modulation of muscle fiber type switching [137-139]. They may be due to increased fatty acid catabolism and mithocondria function in muscle and adipocytes [140]. PPAR□/□ activation also shows anti-inflammatory properties by inhibition of macrophage activation [80, 141].

In particular, it was showed that PPAR□/□ activation leads to an increased glucose utilization in mice liver, as evidenced by the fact that adPPAR□/□ mice had lower fasting glucose levels compared with controls [80]. PPAR□/□ increases through the activation of AMPK, glycogen synthesis and lipogenesis; the ensuing increase of monounsaturated fatty acids (MUFAs) is in turn activator of PPAR□/□ that may protect the liver from free fatty acid-mediated lipotoxicity and inflammation [72]; PPAR□/□ also sustains hepatic glucokinase (GK) levels leading to glycogen accumulation after fasting [72]. PPAR□/□ induces glucose-utilization in hepatocytes by direct and indirect transcriptional mechanisms [72]. The induced lipogenic activity suggests a PPAR□/□ role in steatosis and steatohepatitis. adPPAR □/□ mice had not liver disease neither in normal nor in high diet, as shown by transaminases normality; adPPAR□/□ mice exhibited decrease of Jun N-terminal kinase (JNK) signaling and inflammatory markers [72]. Free fatty acids cause lipotoxicity, which induces inflammatory response; it is possible that PPAR □/□, inducing partitioning of fatty acids for triglyceride synthesis, protects from free fatty acids damage. Indeed, in hepatocytes, PPAR□/□ suppresses fatty acid-induced JNK activation and increases insulin-stimulated Akt phosphorylation; this may be the cause of the improved insulin tolerance test observed in high fat-fed adPPAR □/□ mice [72]. adPPAR□/□ mice livers contain more MUFAs and less saturated fatty acids [72]; therefore, PPAR□/□ may induce free fatty acid storage and/or convert hepatotoxic lipids into less toxic or protective forms. PPAR-beta/delta activity is associated with AMPK activation [76]. AMPK suppresses lipogenesis and glycogen synthesis [142, 143]. Probably, AMPK pathway acts as a negative feedback for PPAR□/□, and this may explain why long term PPAR□/□ treatment do not produce lipid accumulation in the liver [138]. PPAR□/□ could function as a nuclear sensor of dietary fats able to control immune response through regulation of metabolic pathways. In fact, PPAR□/□ produces MUFAs which, in turn, activates macrophage or Kupffer cells PPAR□/□ to modulate immune response [72]. So, the expression of inflammatory markers, as TNF□ or IFN□, is reduced [72].

Therefore, PPAR□/□ activation exerts multiple functions such as sustaining a program of macrophage and Kupffer cell activation in metabolic tissues (in liver it prevents steatohepatitis), suppressing tissue inflammation, increasing oxidative lipid catabolism in the liver, ameliorating serum lipid profiles and global insulin sensitivity, favoring weight loss in obesity [74].

Interestingly, PPAR□/□ may upregulate PPAR□ expression, thus, indirectly, stimulating lipid metabolism and increasing the synthesis of HDL, apoAI, apoA-II and apoA-III [137].

3.3. PPAR□ in Hepatic Stellate Cells

Upon hepatic injury, HSCs become activated and undergo transdifferentiation from non-proliferating cells, storing vitamin A and lipid droplets, to myofibroblasts producing collagen, particularly type I. These myofibroblasts play a pivotal role in liver fibrogenesis increasing extracellular matrix. HSCs activation is mediated by several cytokines and chemokines [144]. PPAR□ is proven to be a key factor in HSCs activation and phenotype alteration [145]; indeed, HSCs activation is characterized by a PPAR□ expression. Ectopic PPAR□ expression or PPAR□ ligands may also bring HSCs back to quiescent form and decrease collagen secretion in vitro and in vivo [4, 19, 17]. Several studies show that PPAR□ manages to keep HSCs in quiescent phase regulating many trascription factors, such as CCAAT/enhancer binding protein (C/EBP), LXR□ and sterol regulatory element-binding proteins-1c (SREBP-1c), which are depleted when HSCs are activated [146]. Moreover, adipogenic transcriptional regulation in HSCs by PPAR□ is important also in packaging of chromatin because DNA methylation inhibitor blocks myofibroblastic transdifferentiation of HSCs and prevents the diminished PPAR□ expression in HSCs [147]. Therefore, PPAR□ is an important factor that helps to maintain HSCs in quiescent form and exerts anti-fibrotic actions in the liver [148]. The precise molecular mechanism underlying the anti-fibrotic actions of PPAR□ is largely unknown, but some mechanisms have been elucidated. Transforming growth factor-□ (TGF□), and particularly TGF□1, is a key mediator implicated in liver fibrosis [144]. Following activation due to liver damage, TGF□1 binds its receptors (T□R1

and T□R2), allows the phosphorylation of Smad2 and Smad3 and permits Smad2/3 to associate with Smad4; the signaling pathway traslocates to the nucleus and initiates the transcription of several genes, including collagen I and III [144]. Smad6/7 represents the inhibition mechanism of this pathway, being able to divide Smad2/3 from the receptor [149]. Activated HSCs express TGF□I and Smad 2, 3, 4 and 7, but Smad7 appears to be silenciated [149]. The TGF□/Smad pathway may play a pivotal role in liver fibrogenesis mediated by activation of HSCs. PPAR□can prevent the function of TGF□/Smad pathway in profibrotic myofibroblasts [150]. PPAR□ inhibits the secretion of connective tissue growth factor (CTGF) induced by TGF□[151]; this suppression can be completely rescued by Smad3 overexpression but not by Smad4 [144]. PPAR□has the ability to divide the bond between the complex TGF-beta1-activated Smads and their response elements, thus reducing collagen I secretion.

Platelet-derived growth factor (PDGF) is another important profibrotic mediator for HSCs activation and hepatic fibrogenesis; PDGF is formed by a disulfide-linked dimeric protein composed by various combinations of four polypeptide chains (A, B, C and D). PDGF exerts its function after binding with its tyrosine kinase receptor PDGF□R and PDGF□R. Quiescent HSCs have not PDGF□R, but, after their activation, HSCs begin to express this receptor and increase their responsivity to PDGF-B [152]. More recently, an implication in liver fibrogenesis for PDGF-C and PDGF-D was demonstrated [153, 154]. PPAR□is involved in opposing PDGF action; PPAR□ ligands or transfection with PPAR□ decrease PDGF-induced human HSCs proliferation in in vitro studies [19, 155]. PPAR□ activation inhibits extracellular factor-regulated kinases (ERK) activity and PDGF-induced c-Fos promoter activity, suggesting that PPAR□ can affect the intracellular transduction signal of PDGF [156].

Hepatocyte growth factor (HGF), a mitogen for hepatocytes, induces cellular growth, motility and morphogenesis and its receptor is identified in c-Met [157]. HGF can prevent liver fibrogenesis. In vivo, in distinct animal models, HGF has proven to be able to reduce HSCs activation and collagen secretion and to facilitate liver recovery after injury [158-160]. Probably, HGF antifibrotic action is due to disruption of TGF□I signaling [161]. PPAR□may induce HGF promoter activity and increase HGF mRNA in fibroblasts [162, 163].

Many studies, in vitro and in vivo, elucidated that leptin is a potent stimulator of HSCs profibrogenic transformation: leptin may induce proliferation, prevent apoptosis, mediate collagen secretion and increase secretion of proinflammatory cytokines in the liver [164-167]. Leptin may induce HSCs phagocytosis, activate Kupffer cells and macrophages and stimulate hepatic sinusoid endothelial cells to produce TGF□ [168]. In vitro, leptin reduces PPAR□gene expression [169], whereas, in vivo, it induces suppression of PPAR□ protein expression in HSCs, probably through leptin-induced ERK1/2 activation [170].

On the contrary, adiponectin has proven to be a beneficial molecule in liver fibrogenesis and inflammation: adiponectin knockout led to develop severe liver fibrosis [171]. Current knowledge about the anti-fibrogenetic effect of adiponectin includes induction of caspase-dependent apoptosis in activated HSCs [172], upregulation of AMPK and inhibition of AKT pathway [173], activation of mitochondrial respiratory chain complexes involving uncoupling protein 2 [174] and recruitment of Kupffer cells [144]. PPAR□ plays a critical role in adiponectin expression and secretion: in humans, an adiponectin promoter PPRE was identified [175] and PPAR□ agonists were able to induce transactivation of adiponectin promoter [176].

Apoptosis has proven to be important in the pathogenesis of liver fibrosis: in fact, fibrogenesis is accompanied by hepatocyte apoptosis [177] and HSCs apoptosis is correlated with fibrosis regression [178]. It was demonstrated that TNF□, a pro-inflammatory cytokine involved in apoptosis extrinsic pathway and in liver fibrogenesis, induces inhibition of PPAR□ activity at post-translational level in HSCs [16]. Other authors studied the PPAR□interaction with death receptor (especially DR5) pathway and with apoptosis triggered by C/EBP-alfa in HSCs, defining the role of PPAR□as a modulator of extrinsic pathway in HSCs apoptosis [144]. PPAR□ also modulates intrinsic pathway of apoptosis in HSCs. Cidea (mithocondrial cell death-inducing DNA fragmentation factor □-like effector A), a proapoptotic factor implicated in mithocondrial apoptotic pathway, is a target gene of PPAR□[179].

Moreover, it has been demonstrated that the expression/activity of PPARs is positively modulated by the nuclear receptor FXR (Farnesoid X Receptor) [180]. These authors identified, in the PPAR□gene promoter, a sequence containing FXR-responsive element (FXRE). The bond between FXR and the promoter sequence leads to PPAR□gene transcription. The same authors also demonstrated the role of FXR-PPAR□crosstalk in inhibiting cytokine production and regulating inflammatory response of HSCs exposed to LPS. The cross-talk between these two nuclear receptors represses, in turn, the synthesis of collagen- and □-SMA expression in activated HSCs [180].

Complex mechanisms, involving acetaldehyde pathway, the release of TNF-□and the activation of NF-kB signalling pathways, inhibit PPAR□ expression during chronic alcoholic liver disease [50].

PPAR-□ expression is downregulated in HSCs isolated from several animal models of liver fibrosis [19]. A number of studies have elucidated that PPAR□ stimulation and expression inhibit HSCs activation and proliferation and, consequently, collagen secretion, both in vitro and in vivo [4]. Indeed, when HSCs go from quiescent to activated phase, PPAR□expression gradually lower; this, strongly indicates the fundamental function of PPAR□in maintaining HSCs in a quiescent phase by controlling a panel of adipogenic transcription factors, (CCAAT/enhancer binding protein LXR□, and SREBP-1c), crosstalking and inhibiting a series of growth factors (TGF□, PDGF, HGF), downregulating metalloproteins (MMP-2, MMP-9) and maintaining a dynamic balance between HSCs proliferative and apoptotic status [4, 5, 144, 146, 181].

Interestingly, it was demonstrated that an adenovirus mediated PPAR□ gene transfer prevents the development and ameliorates steatohepatitis and fibrosis in mice fed with methionine choline deficient diet [181, 182].

Further studies in vitro demonstrated that activated HSCs can be phenotypically and functionally reversed to quiescent HSCs by restored expression (via an adenoviral vector) or stimulated expression (via a selective agonist) of PPAR-□ [98, 183].

3.4. PPARs in Liver Sinusoidal Endothelial Cells (LSEC)

Capillarization of hepatic sinusoid (with losing of fenestration) in cirrhosis has been a well-known condition since 1963 [184] but only little knowledge exists on the control and reversal of this phenomenon.

Previous studies demonstrated a protective role of PPAR□ on endothelial function [185-187]. Interestingly, Rodrìguez-Villarupla and colleagues performed an elegant study in a murine model in cirrhosis evaluating the effects of PPAR□ activation with fenofibrate [188]. They found a reduction of portal hypertension and an improvement of architectural abnormalities in rats treated with fenofibrate compared to controls. Fenofibrate treated rats showed a marked reduction in portal hypertension and fibrosis and an increase in nodule size (this findings correlate with better prognosis in cirrhotic patients, [189]). A reduction in collagen I mRNA, □SMA and COX-1 protein expression and an increased availability of NO was also demonstrated [189].

Moreover, Xie G and colleagues found an interesting role of VEGF and NO in liver endothelial homeostasis [190]. The study demonstrated that maintenance of liver sinusoidal endothelial cells (LSEC) differentiation in vitro requires VEGF stimulated NO working through soluble guanylate cyclase (sGC) activation plus VEGF working through an NO-independent pathway.

In vivo sGC can reverse LSEC capillarization in cirrhosis with a subsequent accelerated reversal of HSC activation and fibrosis [190]. The sGC activator has limited effect in vitro on HSC activation; if sGC activator is administered in co-culture of activated HSCs plus capillarizated LSEC, there is an almost complete reversal of HSC activation and LSEC capillarization. VEGF-stimulated cGMP pathway is necessary but not sufficient to maintain LSEC differentiation [190]. VEGF activates multiple pathways such as mitogen-activated protein kinase (MAPK), focal adhesion kinase (FAK), phosphatidylinositol 3-kinase (PI3K/Akt), Phospholipase C-□(PLC-□ [191]. Although VEGF is a key factor in maintaining LSEC homeostasis, it is increased in cirrhosis, suggesting that capillarization is due to distruption of signalling downstream VEGF. In fact, restoration of cGMP levels in vivo showed to be sufficient to normalize LSEC phenotype, allowing to hypothesize that a defect in NO/sGC/cGMP pathway is responsible for LSEC capillarization.

Therefore, PPAR□may be an important and useful target for future therapeutic strategy on LSEC.

4. PPARs STIMULATION STRATEGIES THERAPY

In the liver of healthy subjects, the process of fibrogenesis is counterbalanced by that of fibrolysis. On the contrary, liver fibrosis begins when this mechanism is dysregulated causing a huge accumulation of extracellular matrix.

Pivotal studies have demonstrated that liver fibrosis is not always an irreversible condition provided that underlying etiological agents are removed, as has been the case with secondary biliary fibrosis, Hepatitis C, Hepatitis B, steatohepatitis, and autoimmune hepatitis [192].

The ability to induce regression of advanced liver fibrosis or cirrhosis open new hope for antifibrotic treatments [193, 194].

Important studies indicate that, after liver injury, a number of bone marrow-derived monocyte/macrophages is recruited at the sites of liver inflammation contributing to myofibroblast population and playing an important role in inflammation, regeneration, remodeling of extracellular matrix and fibrogenesis [195, 196]; however, HSCs contributing to > 80% of the collagen producing cells, are still considered to be the most important source of myofibroblasts in liver fibrosis and also the natural target of anti-fibrotic therapy [197, 198]. Indeed, activated HSCs may transdifferentiate into myofibroblasts or revert to quiescent HSCs [192].

Due to the key role in contributing to regulate phenotype of HSCs, deeper researches in the field of molecular biology have been focused on PPARs in liver fibrosis; since PPARs are important regulatory transcription receptors in the liver [1], they emerge as fundamental targets of anti-fibrogenic treatments. Indeed, they may modulate several metabolic and inflammatory pathways by responding to signals through ligand activation of transcription. It is quite evident that a significantly decreased PPAR□ expression favours HSCs activation, whereas ectopic PPAR□ expression or PPAR□ ligands inhibit HSCs activation and favour the phenotypic reversal of activated to quiescent HSCs, in culture [4, 192, 146].

Although long-term studies are needed to confirm efficacy and safety of PPARs agonists, several studies seem to open more than one perspective in the field of antifibrotic therapy of the liver disease using PPARs agonists.

According to some experts, since myofibroblasts or activated HSCs are involved in synthesizing collagen in extracellular matrix, the aim of antifibrotic therapy is to induce apoptosis of activated myofibroblasts or reverse phenotype from myofibroblast or activated HSCs to quiescent HSCs [192].

To date, two principal classes of clinical drugs that target PPAR□ and PPAR□ are known: they are fibrates and thiazolidinediones which, respectively, decrease circulating fatty acids and triglycerides and increase insulin sensitivity in type II diabetes [199].

Here, we analyze clinical perspectives and feasibility in using agonists of PPARs as antifibrotic liver treatment.

4.1. PPAR□ Agonists

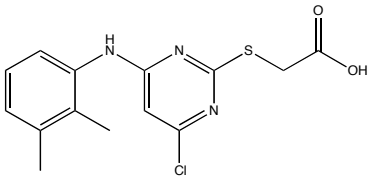
A key function of PPAR□is to control liver inflammation by regulating acute phase protein in hepatocytes and to reduce triglyceride storage and adipose-tissue-derived circulating factors thus increasing insulin sensitivity [200] and ameliorating the level of liver fibrosis.

PPAR has its major impact on regulation of genes encoding enzymes involved in mitochondrial and peroxisomal fatty acid oxidation in human hepatocytes [201].

Several oncogenes (c-Ha-ras, jun and c-myc) and genes linked to cell cycle (control immediate early gene, rZFP-37) are also known to be responsive to PPAR induction [202]; indeed, PPAR is a key actor in the process of peroxisome proliferation, hypertrophy, cell proliferation and hepatocarcinogenesis as demonstrated in primary hepatocytes culture and in animal models [201]. PPAR stimulation may suppress both spontaneous and induced hepatocyte apoptosis [202] through TNF mediator; activation of the MEK/ERK signalling pathway as well as the p38 MAP kinase pathway and the transcription factor NF B are all important mechanisms that suppress hepatocyte apoptosis in response to PPAR agonists [202-204]. However, no increased risk of liver cancer has been hypothesized in humans due to the low level of expression of PPAR and to the rare appearance of mutant forms compared to those observed in animal models [202].

The principal exogenous PPAR agonists are:

- PPAR agonist Wy-14,643 (3) which, by preventing intrahepatic lipid accumulation, inhibits the development of methionine and choline deficient diet-induced steatohepatitis and reduces the level of liver fibrosis [205, 206]. In particular, it was observed that Wy-14,643, upregulating a set of target genes that promote fatty acid breakdown in the liver, was able to counteract hepatic triglyceride and lipid peroxidation accumulation and this rapidly (within 12 days) reversed steatohepatitis [206].



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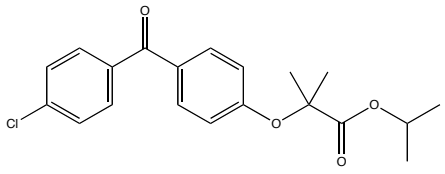
Interestingly, the increased ability of the liver to break down existing lipoperoxides strongly counteracts hepatic inflammation and fibrosis [207]. The precise mechanisms through which Wy-14,643 decreases liver fibrosis is a reduced activation of HSCs and Kupffer cells by means of a diminished release of cytokines by macrophages and other leukocytes [206].

The administration of WY14,643 in ethanol-fed mice also restored the induction of PPAR target genes thus indicating that this agonist prevents the effect of ethanol on PPAR minimizing the post-translational modifications of the PPAR DNA binding domain by acetaldehyde, improving fatty acid oxidation and preventing liver steatosis [208].

- To date, fibrate drugs fenofibrate (4), gemfibrozil (5), benzafibrate (6), ciprofibrate (7), and clofibrate (8) that are ligands of PPAR receptor, have been used with success as adjunct therapies to decrease triglyceride and low density lipoprotein (LDL)-cholesterol levels and increase HDL-cholesterol levels [209, 210].



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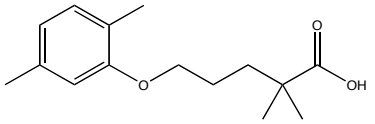

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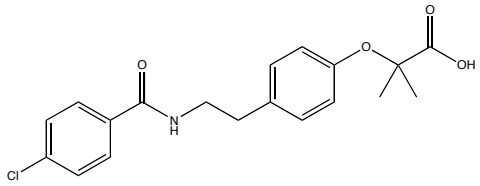

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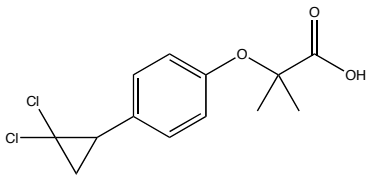

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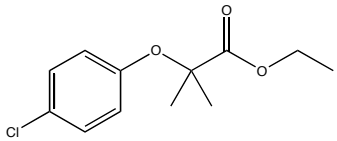

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Fibrates activate PPAR that stimulates the oxidation of free fatty acids in the liver, consequently diminishing the synthesis of triglycerides and triglyceride-rich lipoproteins [211, 212].

Activated PPAR also inhibits the synthesis of apolipoprotein (apo) C-III (that delays the catabolism of triglyceride-rich lipoproteins) and favors the expression of the gene for lipoprotein lipase [213, 214]; this latter enzyme promotes hydrolyzation of triglycerides and phospholipids in triglyceride-rich lipoproteins in plasma. Fibrates increase the level of HDL by [215].

- enhancing the expression of the genes for both apo A-I and apo A-II, the 2 main apolipoproteins of HDL [216, 217]
- increasing cell cholesterol efflux secondary to an induction of cell ABCA1 expression [218]
- decreasing SR-B1 in the liver [219].

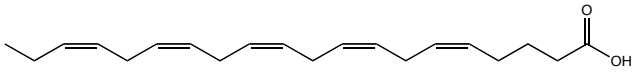
Fibrates also lower LDL-C levels, decrease the concentration of triglyceride-rich lipoprotein remnants and increase the LDL particle size [220-222].

The PPARα agonist clofibrate reduces the amount of fat in the liver and decreases the necroinflammatory injury in ethanol-fed rats [223].

The PPARα agonist fenofibrate exerts multiple cellular functions and has a key role in the protection from oxidative stress induced injury.

Furthermore, fenofibrate was demonstrated to have protective preischemic properties significantly attenuating the ischemic/reperfusion liver injury through the reduction of the oxidative stress markers and of the level of inflammatory mediator TNF-α [224]. This result was obtained thanks to its ability to lower the release of lipid peroxidation products and to enhance the expression of antioxidant enzymes such as superoxide dismutase and catalase in the rat liver.

Of note, the dietary supplementation with the n-3 polyunsaturated fatty acids, with eicosapentaenoic acid (9) and with docosahexaenoic acid (10) to a rat model of hepatic ischemia-reperfusion-injury favoured the activation of PPARα and the inhibition of NF-kB signalling pathway and of transcription of pro-inflammatory cytokines, thus suppressing the hepatic ischemia-reperfusion-injury [225].



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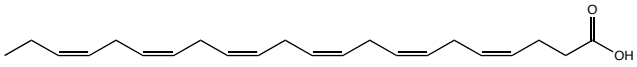

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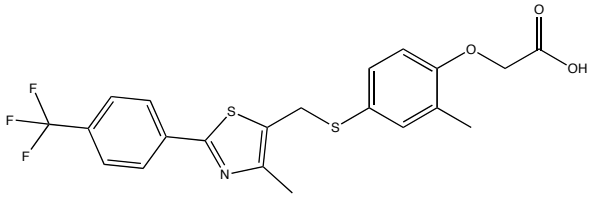
An interesting research, based on the structure-activity relationship, showed that steric bulkiness and position of the distal hydrophobic tail part are critical for agonistic activity and selectivity of PPARα [226]; in this study, performed on rat fed with non alcoholic fatty liver disease induced by choline deficient high-fat diet, PPARα-selective activation prevented or ameliorated liver dysfunction and delayed the progression of fatty liver to fibrosis [226].

New advancements in this field might help to select the best compounds able to interact with PPARα with the aim of more benefit and safety.

4.2. PPAR α/β Agonists

Several PPARα/β agonists are known: GW501516 (11), L165041 (12), GW0742 (13), KD3010 (14), GW1514 (15), Compound F (16), and GW610742 (17) [70].



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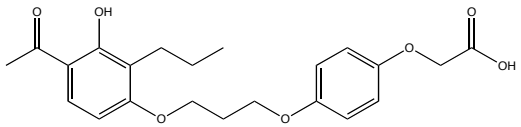

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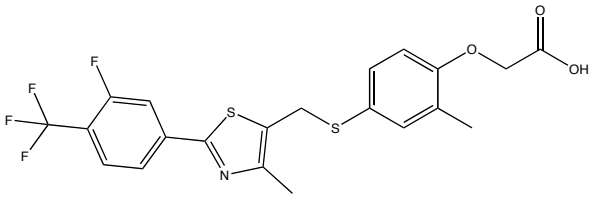

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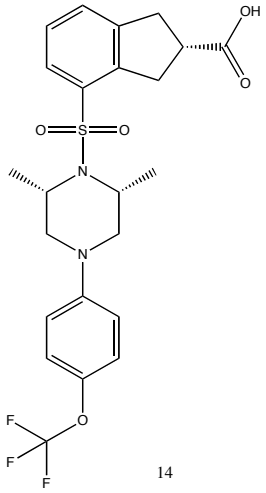

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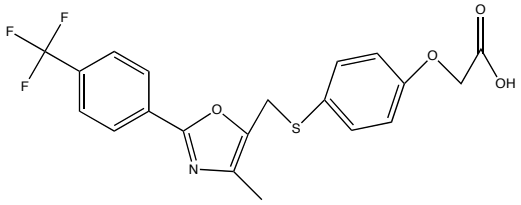

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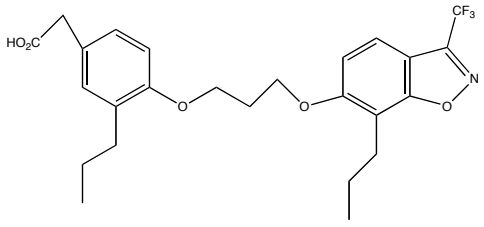

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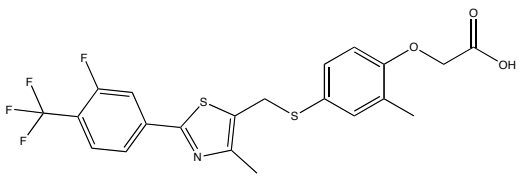

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- Treatment with the high-affinity PPAR□/□ agonist (GW501516) enhances HDL levels [137].

A two-week treatment with GW501516 also induces a reduction in liver fat content and in plasma triglycerides (due to the reduced triglyceride production from the liver) [227].

Interestingly, after a two-week treatment with GW50 1516, diabetic db/db mice affected by insulin resistance and glucose intolerance, have an improvement of hepatic and peripheral insulin sensitivity, without weight loss [228]. An increased glycolysis, a highly activated pentose phosphate pathway as well as an enhanced fatty acid synthesis in the liver, are all regulatory molecular mechanisms through which PPAR□/□ activation reduces hepatic glucose output [228].

GW501516 was further demonstrated to be effective in MSG mice affected by metabolic syndrome. This compound improved insulin sensitivity, serum insulin and leptin levels, glucose and lipid metabolism [227]. These authors concluded that pharmacological activation of PPAR □/□ may be a useful preventive and therapeutic strategy in metabolic syndrome [229].

Therefore, PPAR□/□ activation shows a pivotal role in maintaining the glucose-lipid homeostasis by stimulating fatty acid oxidation, inhibiting glucose and VLDL secretion from the liver, increasing circulating HDL levels; furthermore, PPAR□/□ regulates the inflammatory activity of macrophages via NF-kB suppressing iNOS and COX2 [230].

- Another PPAR□/□ agonist, L-165041, raises plasma cholesterol concentrations and HDL levels in insulin-resistant db/db mice but has no effect on either glucose or triglycerides [231].

In ethanol-fed rats, the elevated ethanol consumption causes the impairment of liver regeneration by inhibiting insulin signaling that mediates hepatocellular DNA synthesis; the administration of L-165041 restored this function attenuating ethanol-induced hepatic injury and improving liver regeneration thus demonstrating to have protective liver effects [232]. This PPAR□/□ agonist also ameliorated hepatic insulin sensitivity by means of the increased insulin receptor binding, the increased signaling downstream through PI3K/Akt, which promotes cell survival, and the reduced DNA damage and lipid peroxidation [232].

Another study based on administrating L-165041, in vitro, on culture of HSCs and, in vivo, on rat model of acute liver injury (not in chronic liver injury), put in evidence the presence of enhanced acute liver toxicity (high levels of PPAR□/□ expression in activated HSCs and low level of PPAR□ expression and adipogenesis) [70]. In contrast with this result, the same authors ascertained, after L-165041 administration, an increased expression of CRBP-I and LRAT (both involved in retinol esterification) during HSCs activation, thus demonstrating an important role of this compound in maintaining adequate vitamin A storage [69]. Since transformation of HSCs in myofibroblasts is commonly associated with loss of vitamin A, the agonist L-165041 might be potentially useful to inhibit HSCs transformation.

- Furthermore, the administration of PPAR □/□ agonist GW0742 in wild-type and in PPAR□/□ -null mice treated with CCl(4) demonstrated to be useful in reducing hepatic toxicity by downregulating expression of proinflammatory genes [233].

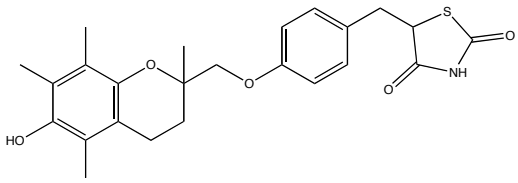
- An interesting dual study on CCl(4) treated mice and mice that underwent cholestatic liver injury by bile duct ligation, showed hepatoprotective and antifibrotic effects of PPAR□/□ agonist KD3010 in comparison with control groups [233]. KD3010 did not decrease HSCs activation nor attenuated the change of their morphology but protected cultured hepatocytes from starvation and CCl(4)-induced cell death, due to the reduced reactive oxygen species production [234].

As demonstrated by an interesting study [235], further progress on the choice of better PPAR □/□ agonists might derive from molecular-structure-activity relationship researches that may test more easily the potency and selectivity of these compounds.

4.3. PPAR□ Agonists

Several therapeutic strategies, based on the use of PPAR-□ agonists able to stimulate inhibition of HSCs activation and proliferation and to favour induction of HSCs apoptosis have proven to be potential anti-fibrotic approaches. PPAR-□ stimulation now represents an important target for anti-fibrotic therapy [4, 5, 16, 19]. Several PPAR□ agonists are known (Fig. 3):

- Thiazolidinediones: troglitazone (18), ciglitazone (19), pioglitazone (20), rosiglitazone (21), netoglitazone (22) and rivoglitazone (23). They are antidiabetic drugs that reduce insulin resistance and structurally derive from clofibric acid (24); they selectively bind to two histidine residues, H323 and H449, of the PPAR□ transcription factor [28]. Generally, the action of thiazolidinediones go against the TGF-□ expression (consequently inhibiting the synthesis of procollagen and the activity of transcription factors AP-1, STAT and NF-kB [97, 236].



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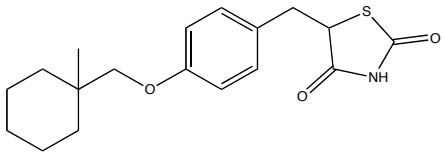

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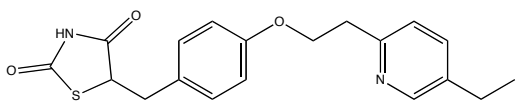

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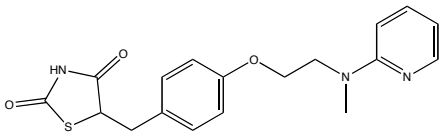

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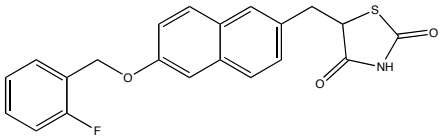

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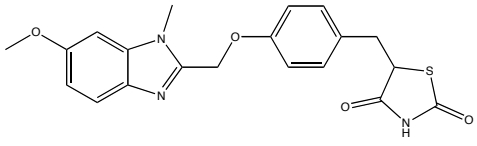

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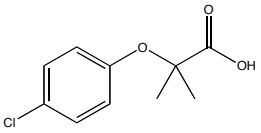

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Also there is the mentioned TZD-induced effect of PPAR□in differentiation of adipose tissue, that stimulates differentiation of small adipocytes (more insulin sensitive) and favors apoptosis of large adipocytes. TZD promotes the PPAR□mediated regulation of GLUT4 [237] and c-Cbl associating protein (CAP) [238].

Due to their efficacy on low insulin resistance, thiazolidinediones were demonstrated to be of benefit in treating liver fibrosis consequent to metabolic syndrome [239].

The PPAR□ agonist troglitazone showed to inhibit, in dose-dependent mode, HSCs proliferation and chemotaxis induced by PDGF and to regulate expression of proinflammatory genes [38].

Another study demonstrated that, only in an adiponectin-mediated manner, troglitazone suppressed upregulation of collagen □I(I) and □SMA mRNA in HSCs isolated from wild-type mice [86].

Ciglitazone regulated, in vitro, the expression of the leptin receptor Ob-R in activated HSCs, whose function is actually to mediate HSCs proliferation; by stimulating PPAR□transcription factor, ciglitazone gave inhibitory effect on leptin-induced HSCs proliferation with a reversion of ERKs activation [240].

Both ciglitazone and troglitazone were abandoned after clinical trials that documented severe liver toxicity and side effects (oxidative stress, mitochondrial damage, accumulation of toxic metabolites, overexpression of genes expressing adipocyte fatty acid binding protein and fatty acid translocase, exacerbation of fatty liver) as well as insurgence of severe liver failure and death [241].

Pioglitazone demonstrated to inhibit hepatic fibrosis caused by CCl(4) and to have a protective role against hepatotoxicity, through inhibition of HSCs proliferation and inflammation [242].

Mice fed with methionine-choline deficient diet treated with adenovirus carrying PPAR□plus Rosiglitazone had a significant reduction of hepatic fibrosing steatohepatitis [243, 181, 182]. It was observed:

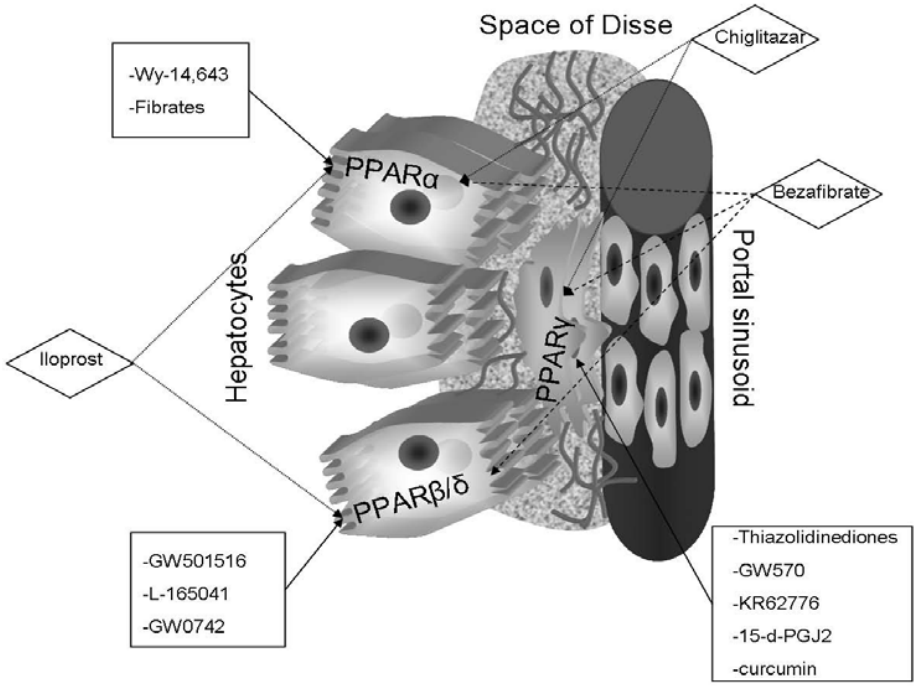


Fig. (3). Schematic view of PPAR agonists and their actions on PPAR□, PPAR□□or PPAR□ or on both dual or pan PPARs.

- a reduction of expression of TNF□, IL-6
- a decrease of serum ALT level and oxidative stress
- a down-regulation of the expression of profibrogenic genes of TGF-□, MMP-2 and MMP-9
- an up-regulation of the expression of adiponectin.

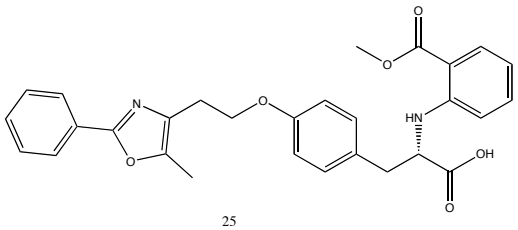
Furthermore, in a murine model of liver fibrosis induced by Schistosoma japonicum infection, rosiglitazone alone or plus praziquantel, reduced inflammation and liver fibrosis by decreasing the hepatic expression of TGF-□1, □-SMA, types I & III collagens [244].

Interestingly, both Pioglitazone and Rosiglitazone caused much less frequent and severe hepatotoxicity than ciglitazone and troglitazone [245].

However, a study on gene expression induced by rosiglitazone on hepatocytes in vitro, showed that many genes involved in pharmacological PPAR targeted functions, were up-regulated including intracellular uptake and binding of fatty acids, hepatic ketogenesis, mitochondrial □-oxidation, peroxisomal □-oxidation, lipogenesis, lipolysis, lipoprotein metabolism, glucose/glycerol metabolism and bile acid biosynthesis and transport [245]. Rosiglitazone was also found to induce an increase of both liver weight and hepatic triglycerides in mice [241].

- Non-Thiazolidinediones insulin sensitizer PPAR□ agonist GW570 (not available, GlaxoSmithKline™) in a dose-dependent manner inhibited HSCs activation and had antifibrotic effects on cultured HSCs and on CCl(4) treated mice and mice that underwent cholestatic liver injury by bile duct ligation [246].

- The PPAR□ agonist GW7845 (25) blocked the TGF□1-mediated activation of Smad3 and the induction of collagen and PAI-1 expression without affecting HSCs proliferation or viability in a study in vitro on adipocytic human HSCs [183]. According to these authors, GW7845 may prevent adipocytic HSCs by acquiring a myofibroblastic phenotype during chronic liver injury [183].



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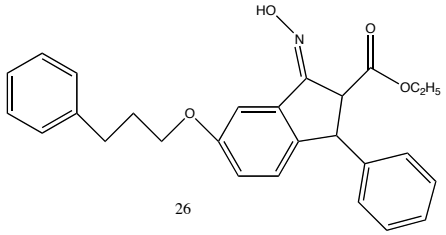
These results were confirmed in another in vitro study on HSCs rat in which GW7845 inhibited the growth of HSCs and TGF□1-induced CTGF expression, thus confirming itself as a potential antifibrotic compound in treating and preventing liver fibrosis [247].

- Another in vitro study showed that the PPAR□ agonist, KR62776 (26), caused apoptosis of activated HSCs cells, decreased the □-smooth muscle actin levels and offered some protection against CCl(4)-induced hepatocellular damage [248].

- the endogenous ligand 15-Deoxy-□^{12,14}-prostaglandin J_2 (15-d-PGJ2) (27) inhibited cell growth of rat HSCs, both through cell cycle arrest (G_0/G_1 phase arrest and prevention of cells from entering the S phase) and an increase in apoptosis; 15-d-PGJ2 also displayed antifbrotic effects through a marked inhibition of TGF□1-induced CTGF expression [249].



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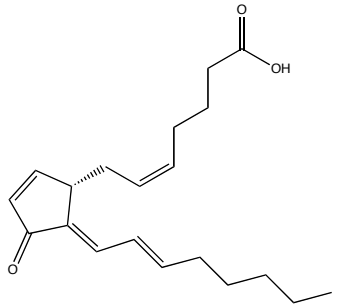

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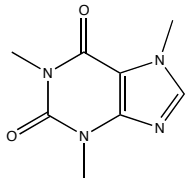
Of note, the authors demonstrated that the methylxanthine derivate caffeine (28) upregulating the expression of PPAR□ in hepatocytes, sensitizes these cells to the well-known inhibitory effect of 15-d-PGJ2 on CTGF expression [249]. The inhibition of TGF□-induced CTGF expression through a PPAR□-dependent mechanism was confirmed in a study on human hepatoma cells [250].



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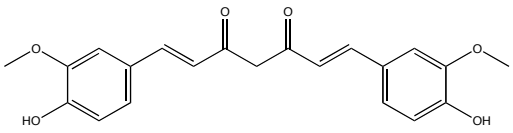
Quite recently, an interesting study, performed on a mouse model of liver injury induced by cholestasis or CCl(4), demonstrated the ability of 15-d-PGJ2 to significantly reduce the recruitment of bone marrow-derived monocyte/macrophage at the sites of inflammation, in a PPAR□ independent manner [251]. No decrease of migration of neutrophils, dendritic or T cells was observed. A significant inhibition of phagocytosis, and cytokine expression and an attenuation of liver inflammation and fibrosis were also documented [251].

- the natural polyphenolic compound curcumin (29) (the main yellow pigment of a popular spice, turmeric, widely used as a food colorant), is well tolerated and has slow toxicity.

No adverse effects have been found in subjects consuming up to 150mg of curcumin daily [252]. Studies on its bioavailability demonstrated a poor absorption and rapid

metabolism resulting in low serum levels, limited tissue distribution and short half-life [252].



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The liver and intestinal mucosa seem to be the principal organs responsible for its metabolism [252].

In humans, curcumin gives an anti-inflammatory response by inhibiting the induction of COX-2 and iNOS; an anticarcinogenesis effect has been also suggested as the result of apoptosis [252].

Curcumin improved both acute and subacute rat liver injury induced by CCl(4) [253]. According to some authors, it was able to prevent acute and subacute liver toxicity of CCl(4) through its antioxidant properties and its ability to inactivate NF-kB and pro-inflammatory cytokine production [254, 255]. Furthermore, benefits for liver from curcumin administration were confirmed in a rat model of cirrhosis induced by CCl(4), where this compound caused an important decrease in GSH, GSH/GSSG ratio and total glutathione produced [256].

The administration of curcumin on culture-activated HSCs inhibited their proliferation and induced apoptosis [124]. This compound significantly inhibited cell growth and suppressed the expression of collagen-□(I), fibronectin and □SMA genes in HSCs [256].

Through a PPAR□manner, curcumin was also found to significantly reduce the expression of two autonomously functioning heterodimers T□RI and T□RII [257] that compose the dimeric polypeptide TGF□ [258]. This leads to TGF□ signaling disruption in HSCs and favours a potent antifibrotic effect. Moreover, PPAR□ activation curcumin mediated inhibits TGF□-induced CTGF expression. According to these authors, the results of the study indicate that PPAR□crosstalks with TGF□signaling and imply that pharmacological intervention via PPAR□ activation can indeed block the profibrogenic TGF□Smad pathway and thereby inhibit HSCs activation and ameliorate hepatic fibrosis [259, 260]. A reduction of PDGF and TGF□was also observed in a rat model of hepatic injury induced by CCl(4), after the administration of curcumin that also attenuated oxidative stress, suppressing inflammation and inhibiting activation of HSCs [261].

According to other authors, curcumin, in a dose dependent manner, induces gene expression of endogenous PPAR□ in activated HSCs through the interruption of PDGF and EGF signaling pathways by inhibiting tyrosine phosphorylation of their receptor and reducing the levels of phosphorylated phosphatidylinositol-3 kinase (PI-3K/AKT), ERK and the JNK [262, 263].

The effects of curcumin were also explored on a murine model of bile duct inflammation and liver damage in cholangiopathy where this compound showed to have anti-fibrotic effects blocking proliferation and activation of portal myofibroblasts by inhibiting ERK1/2 in a PPAR□manner [264].

Interestingly, administration of curcumin to mice fed with a methionine- and choline-deficient diet was able to reduce intrahepatic expression of fibrogenic genes and liver fibrosis; after its administration in cultured HSCs, secretion of tissue inhibitor of metalloprotease and generation of ROS were also diminished [265].

Another interesting study in a rat model of liver fibrosis induced by CCl(4) was planned to search whether curcumin could have antioxidant effects increasing enzymes such as APE1. It was found that, after curcumin administration, liver injury and oxidative stress, together with TNF□, NF-kB and HSCs activation, decreased; concomitantly, a re-elevation of APE1 mRNA and protein levels was noted, thus demonstrating a role of this antioxidant pathway activated in PPAR□ manner by curcumin [266].

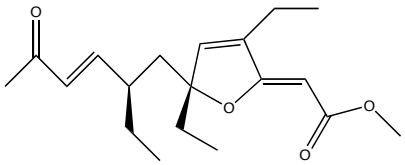
A recent interesting study showed that curcumin was not only able to regulate HSCs activation but also the cell cycle progression of damaged hepatocytes inducing them to undergo apoptosis by up-regulating its P53 level expression [267].

Of great importance, a recent study showed that curcumin inhibited the receptors of advanced glycation end-products thus decreasing activation of HSCs, by means of PPAR□activation [268, 269].

Since curcumin is safe for human consumption, it may have a beneficial role in alcoholic liver disease, in acute liver injury, in chronic liver diseases.

Interesting molecular studies have clarified the existence of several binding modes of ligands to the target protein; this may result in new clues for improving the binding affinity and selectivity of PPAR□[270] thus ameliorating the ability to treat liver fibrosis.

- a new class of PPAR□ligands from the marine environment was discovered in a Marine Sponge, Plakinastrella mamillaris, from Fiji islands: they might be potential agents in the treatment of fibro-inflammatory disorders [271]. From the isolation and molecular characterization of a library of 13 oxygenated polyketides, the authors focus their interest on 3 of these molecules: gracilioether B (30), gracilioether C (31) and Plakilactone C (32) [271]. These molecules can activate PPAR□with a potency of 20-90 fold less than that of rosiglitazone, but with a very similar efficacy in terms of receptor transactivation (approximated 80%). These three molecules increase the expression of SCD-1 in liver cells (SCD1 catalyzes the rate-limiting reaction of mono-insatured fatty acid and plays an important role in fatty liver) and up-regulate PEPCK (a rate-limiting enzyme involved in gluconeogenesis) [271]. Gracilioether C and plakilactone C, but not gracilioether B, are able to induce expression of CD36, a scavenger receptor involved in the hepatic reuptake of oxidized lipoprotein.



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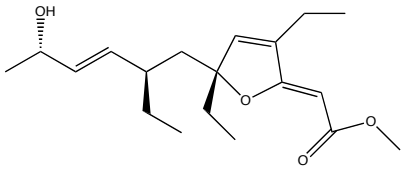

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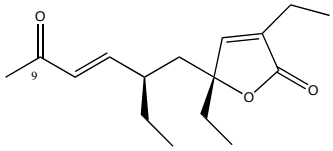

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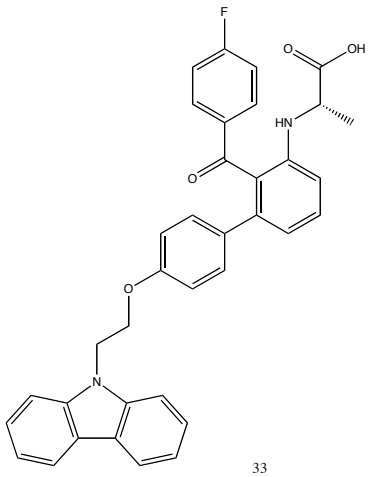
In contrast with the action of gracilioether B and plakilactone C, gracilioether C activates PPARγ in a non-covalent fashion and suppresses production of IL-6 and MCP-1 similarly to the rosiglitazone, thus allowing the hypothesis that it could become an interesting anti-inflammatory drug [271]. Further studies on these molecules may promise interesting results.

4.4. Dual or Pan PPARs Agonists

Dual or pan PPAR agonists, that are PPAR ligands, able to bind two or more PPAR isoforms, thus acting simultaneously on insulin resistance, dyslipidemia and obesity, have been proposed for several years [272].

The summation of benefit findings of each one of these PPARs agonists might help to treat simultaneously both hyperglicemia and obesity and dyslipidemia and then to have beneficial effects on liver fibrosis.

Chiglitazar (33), a PPARγ/δ agonist, by suppressing the expression of genes for the key gluconeogenic enzymes PEPCK and G-6-Pase and upregulating mRNA expression of genes involved in NEFA oxidation, demonstrated to reduce insulin resistance and to improve glucose tolerance and lipid profiles in monosodium L-glutamate obese rats [273]. Unfortunately, this study does not report data on liver fibrosis.



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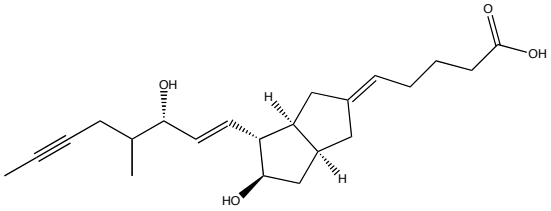
According to some authors, dual PPARα/γ agonists might be useful in patients with non-alcoholic fatty liver disease but more data are necessary on long-term safety, efficacy and impact on liver related histologic outcomes of these compounds [274]. Bezafibrate, an old and well known fibric acid, is the first clinically tested pan PPARs (PPARαγδ) activator that has demonstrated to lower cholesterol, triglyceride, glucose and improve insulin resistance and HDL cholesterol, maintaining a good safety profile [272].

Of great importance, bezafibrate, recently tested in a model of obese mice induced by monosodium glutamate treatment, was demonstrated to have beneficial effects on macro-and microvesicles in hepatocytes and to reduce non-alcoholic fatty liver disease activity score [275].

An important structural and functional study on receptor-ligand interactions showed that the prostacyclin analog iloprost (34), could strongly interact with PPARγ and PPARα/γ Interestingly, two unique hydroxy groups from iloprost, formed hydrogen bonds with Thr-279 and Ser-280 of PPARγand with Thr-252 and Thr-253 of PPARα/γ[276].



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This biochemical detailed study is critical for opening new opportunities in treating several diseases and also liver fibrosis. Iloprost is a well known and safe medical compound, analog of a physiological mediator derived from prostanoids (metabolites of arachidonic acid through the action of cyclooxygenase) and endowed with anti-platelet and arterial vasodilator abilities [277]. Iloprost is able to maintain vascular endothelial homeostasis regulating portal flow volume, hepatic microcirculation and acting as a local hormone to control HSCs function by means of specific cellular receptors [(IP, a transmembrane G-protein coupled receptor) and PPARγand PPARα/γ] [278, 5, 279].

It is now clear that the prostacyclin actions in ameliorating hepatic content of glutathione and hepatocyte mitochondrial function [280, 281] as well as in favouring adipocyte differentiation of HSCs, thus maintaining them in a quiescent phase, might depend on its ability to bind PPARγand PPARα/γ

Interestingly, since hypoxemia aggravates steatohepatitis and liver fibrosis in rats fed with a choline-deficient high-fat diet [282] due to vulnerability of fatty hepatocytes to anoxic injury [283], the ability of iloprost to ameliorate hepatic perfusion might be useful to slow down the development of steatohepatitis and liver fibrosis [284-286].

Finally, after a global analysis of gene regulation by PPARγ and PPARγ δ agonists in human hepatocytes, emerged that a large number of target genes are regulated in common by PPARγγand PPARγagonists [245]; therefore, a large inter-individual and unpredictable response of patients to these compounds may be expected [245].

Moreover, other dual or pan PPARs exist but they have been discontinued because of severe side effects including renal failure, fibrosarcomas, urinary tract cancer and anemia [287].

5. CONCLUSIONS

PPARs are transcription factors that belong to the nuclear receptor superfamily; of the three known isotypes, PPAR□ is principally assigned the task of regulating fatty acid □-oxidation, PPAR□/□ acts prevalently on triglicerides metabolism, on LPL, regulates inflammatory response and may upregulate the activity of PPAR□, PPAR□ increases insulin sensitivity and regulates triglyceride storage in adipose tissue and maintains HSCs in a quiescent phase.

To date, PPAR□ and PPAR□ are target to develop more and more effective therapeutic strategies against steatohepatitis and insulin resistance, respectively, whereas PPAR□/□ promises to become an interesting therapeutic target against metabolism of triglycerides, in the near future.

Given the fact that all three PPARs are closely involved in the pathogenesis of liver fibrosis, it is intriguing to think that they might become common part of a therapeutic strategy against liver fibrosis.

The possibility of using medical compounds that simultaneously act against two or pan PPARs, already exists. Further studies are, however, needed to search potential usefulness of these therapeutic strategies, warding off the threat of insurgence of toxicity or side effects. Therefore, it is important to plan clinical studies that mainly focus on safety of these medical compounds.

Moreover, some help to reach a better affinity and selectivity of medical compounds versus PPARs might come from the interesting studies performed with X-ray crystallographic analysis; these have shown that the high-resolution crystal structures of the PPARs complexed with these agonists will provide the structural basis for specific and versatile binding mode of these ligands [288, 289]; they also might favour further development of drugs treating metabolic diseases and thus fibrosis.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

Declared none.

ABBREVIATIONS

ACOX1	=	Acyl-CoA oxidase 1
ADD-1/SREBP-1	=	Adipocyte determination and differentiation factor 1/sterol response element binding protein 1
AF	=	Activation Function Region
AP-1	=	Activator Protein-1
aP2	=	Adipocyte fatty acid binding protein
APMK, MAPK	=	Mitogen-activated protein kinase
ApoA	=	Apolipoprotein A
ApoC	=	Apolipoprotein C
BMI	=	Body mass index
C / EBP	=	CCAAT / enhancer binding protein
C/EBP-□, -□, and □	=	C/EBP transcription factors
CARM1	=	(Coactivator-associated arginine methyltransferase 1
CCl(4)	=	Carbon tetrachloride
Cidea	=	Mithocondrial cell death-inducing DNA fragmentation factor alpha-like effector A
COUP-TFII	=	COUF Transcription factor 2
COX	=	Cyclooxygenase
CRBP-I	=	Cellular retinol-binding protein, type 1
CTGF	=	Connective tissue growth factor
ECM	=	Extracellular matrix
EGF	=	Epidermal growth factor
ERK	=	Extracellular factor-regulated kinases
ERK	=	Extracellular signal-regulated kinase
GK	=	Glucokinase
GLUT4	=	Insulin-responsive glucose transporter
GSH	=	Glutathione
GSSG	=	Glutathione disulfide
HDL	=	High density lipoprotein
HNF	=	Hepatocyte nuclear factor
HSC	=	Hepatic Stellate Cells
IL	=	Interleukin
iNOS	=	Inducible nitric-oxide synthase
JNK	=	c-Jun N-terminal kinase
LPL	=	Lipoprotein lipase
LRAT lecithin	=	Retinol acyltransferase
LTB4	=	Leukotriene B4
LXR□	=	Liver X receptor □
MCP	=	Monocyte chemotactic protein 1
MED	=	Mediator complex
MFP1/L-PBE	=	Hydratase-dehydrogenase multifunctional/bifunctional enzymes
MMP	=	Metalloprotein
MUFA	=	Monounsaturated fatty acid

N-CoR	=	Nuclear corepressor
NF-kB	=	Nuclear factor-light-chain enhancer of activated B cells
NR	=	Nuclear Receptor
PAI-1	=	Plasminogen activator inhibitor-1
PBP/MED1	=	PPAR-binding protein/TRAP220/DRIP205/ mediator subunit 1
PDGF	=	Platelet-derived growth factor
PEPCK	=	Phosphoenolpyruvate carboxykinase
PGC-1□	=	Peroxisome proliferator-activated receptor-□coactivator 1□
PI-3K/AKT	=	Phosphorylated phosphatidylinositol-3 kinase
PPAR	=	Peroxisome proliferator-activated receptor
PPRE	=	(Peroxisome proliferator response element)
PRIC	=	PPAR□-interacting cofactor
PRIP/NCoA6	=	Nuclear receptor coactivator 6 interacting protein
PTL	=	Pancreatic Trygliceride Lipase
RIP140	=	Receptor Interacting Protein 140
ROS	=	Reactive Oxygen Species
RXR	=	Retinoid X receptor
SCD-1	=	Steaoryl- CoA desaturase-1
sdLDL	=	Small dense LDL
Smad	=	Small mother against decapentaplegic
SMRT	=	Silencing mediator for retinoid and thyroid hormone receptors
SRC1/p160	=	Steroid receptor coactivator 1, p160 family
SREBP-1c	=	Sterol response element binding protein 1c
T-betaR	=	TGFbeta receptor
TG	=	Triglyceride
TGF	=	Transforming growth factor
TNF	=	Tumor necrosis factor
TNF□	=	Tumor necrosis factor
T□RI	=	Transforming growth factor-□ type-I receptor
VLDL	=	Very Low density lipoprotein
□SMA	=	□-smooth muscle actin
□HNF4-RE	=	□hepatic nuclear factor 4 regulatory element

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