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**MINIREVIEW**

# A role of peroxisome proliferator-activated receptor $\gamma$ in non-alcoholic fatty liver disease

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**Abstract**

Non-alcoholic fatty liver disease is becoming a major health burden, as prevalence increases and there are no approved treatment options. Thiazolidinediones target the nuclear receptor peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ) and have been investigated in several clinical trials for their potential in treating non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). PPAR $\gamma$  has specialized roles in distinct tissues and cell types, and although the primary function of PPAR $\gamma$  is in adipose tissue, where the highest expression levels are observed, hepatic expression levels of PPAR $\gamma$  are significantly increased in patients with NAFLD. Thus, NAFLD patients receiving treatment with PPAR $\gamma$  agonists might have a liver response apart from the one in adipose tissue. Owing to the different roles of PPAR $\gamma$ , new treatment strategies include development of compounds harnessing the beneficial effects of PPAR $\gamma$  while restricting PPAR $\gamma$  unwanted effects such as adipogenesis resulting in weight gain. Furthermore, dual or pan agonists targeting two or more of the PPARs have shown promising results in pre-clinical research and some are currently proceeding to clinical trials. This MiniReview explores adipose- and liver-specific actions of PPAR $\gamma$ , and how this knowledge may contribute in the search for new treatment modalities in NAFLD/NASH.

**KEYWORDS**

NAFLD, NASH, pharmacology, PPAR $\gamma$ , TZDs

## 1 | INTRODUCTION

The global prevalence of non-alcoholic fatty liver disease (NAFLD) has reached 25% of the adult population and continues to rise.<sup>1</sup> The increasing disease frequency reflects the high energy intake and sedentary lifestyle characteristics of modern day living, fuelling a cluster of detrimental lifestyle-associated diseases including NAFLD.<sup>2</sup> NAFLD is closely linked to diet-induced dyslipidaemia, metabolic co-morbidities such as dysregulated glucose and lipid metabolism in turn promoting obesity, type 2 diabetes and cardiovascular

diseases.<sup>2,3</sup> The term NAFLD covers a wide range of hepatic disease states ranging from bland steatosis to non-alcoholic steatohepatitis (NASH) with developing hepatic fibrosis, which may progress and ultimately lead to cirrhosis and increased risk of hepatocellular carcinoma<sup>2,4</sup>. Although NAFLD and NASH represent a major burden to the patient and the supporting health system, there is currently no approved pharmacotherapy targeting the disease, emphasizing the current need for novel intervention strategies.

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In the quest of discovering relevant treatment targets, peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ) and the synthetic PPAR $\gamma$  agonists thiazolidinediones (TZD; e.g. rosiglitazone and pioglitazone) have been the subject of increasing attention.<sup>5,6</sup> Large randomized controlled clinical trials have reported that both rosiglitazone and pioglitazone improve NAFLD-related hepatic steatosis and, in the case of pioglitazone, also hepatic inflammation and to a lesser extent fibrosis (Table 1).<sup>7–13</sup> However, TZD treatment has also been associated with weight gain and fluid retention, limiting its application and potentially reducing patient compliance.<sup>7–10</sup> This review elaborates on the role of PPAR $\gamma$  in adipose and liver tissues, addressing how PPAR $\gamma$  expression and/or activation may affect different cell types and signalling pathways, and how this may be exploited in a therapeutic setting.

## 2 | PPAR $\gamma$ IN ADIPOSE TISSUE

PPAR $\gamma$  is a transcription factor and part of a nuclear receptor family comprised of PPAR $\gamma$ , PPAR $\alpha$  and PPAR $\delta$  (also known as PPAR $\beta$ ).<sup>6</sup> Expression is highest in adipocytes, where PPAR $\gamma$  functions as an inducer of adipocyte differentiation.<sup>14,15</sup> TZDs have significant anti-diabetic properties in vivo, mediated—at least in part—through increased insulin sensitivity and the selective activation of PPAR $\gamma$  in adipose tissue.<sup>16,17</sup> By promoting adipose tissue formation, PPAR $\gamma$  paradoxically acts as an insulin sensitizer, even though excess adiposity and obesity is commonly associated with diabetes and insulin resistance.<sup>18</sup> This apparent discrepancy involves the generation of metabolically dysfunctional adipocytes during chronic dyslipidaemia, often accompanied by obesity. Dysfunctional adipose tissue is characterized by hypertrophic tumour necrosis factor  $\alpha$  (TNF $\alpha$ ) producing adipocytes with enhanced rates of lipolysis due to insulin resistance.<sup>19</sup> The enhanced lipolysis increases the release of free fatty acids (FFAs), which may proceed to be ectopically stored, for example, in the liver, leading to steatosis and lipotoxicity, in turn progressing to NASH and cirrhosis.<sup>4,20</sup> PPAR $\gamma$  activation mitigates this vicious circle by promoting the formation of insulin-sensitive adipose tissue dominated by small adipocytes, which can act as a reservoir for excess FFAs thereby potentially preventing lipotoxicity in other tissues and organs (Figure 1).<sup>15,19</sup>

In adipocytes, PPAR $\gamma$  modulates an array of target genes involved in lipid uptake and storage, inflammatory cytokine production and the release of insulin-sensitizing adipokines.<sup>15</sup> Adipocyte lipid uptake is regulated in part by cluster of differentiation 36 (also known as fatty acid translocase), adipocyte protein 2 and lipoprotein lipase, all of which are up-regulated by PPAR $\gamma$  in response to TZD treatment (Figure 1).<sup>21–23</sup> Following uptake of FFAs,

PPAR $\gamma$  activation up-regulates phosphoenolpyruvate carboxykinase, which provides the glycerol backbone for esterification and storage of triglycerides, promoting formation of intracellular lipid vesicles and, consequently, protection from FFA-induced lipotoxicity (Figure 1).<sup>24</sup>

Adipose tissue not only serves as a passive storage site for lipids but also as a recognized endocrine tissue, enabling local and systemic signalling and tissue crosstalk, for example, by the release of cytokines such as TNF $\alpha$  and adiponectin.<sup>25</sup> In the liver, circulating adiponectin activates AMP-activated protein kinase and subsequently induces fatty acid oxidation while lowering gluconeogenesis and insulin resistance (Figure 1).<sup>26</sup> Expectedly, treatment of *ob/ob* mice with recombinant adiponectin improved hepatic steatosis and decreased hepatic TNF $\alpha$  expression.<sup>27</sup> In accordance, full length adiponectin ameliorated hepatic fibrosis in mice fed a NAFLD promoting methionine- and choline-deficient (MCD) diet, supporting a direct effect of adiponectin on key components of progressive NAFLD.<sup>28</sup> Thus, adiponectin would seem a relevant target point in the treatment of NAFLD; however, the extensive post-translational modifications and a large range in circulating normal physiological levels (0.5–30  $\mu\text{g}/\text{mL}$  plasma) have so far limited the applicability of adiponectin as a commercially available therapeutic tool.<sup>27,29,30</sup> Consequently, induction of adiponectin expression and release through up-regulators such as TZDs remain an option to harness the beneficial effects of this adipokine.<sup>29,30</sup> Randomized, placebo-controlled clinical trials<sup>9,13</sup> as well as experimental data from a systematic review<sup>30</sup> report an increase of adiponectin levels in response to TZD treatment in parallel with an improvement of hepatic steatosis. This suggests adiponectin as an important factor in TZD-mediated effects. In a study using adiponectin null mice, TZDs were found to be dependent on adiponectin in improving glucose tolerance, providing evidence of adiponectin as a key player in TZD treatment.<sup>31</sup> Whether adiponectin dependence translates to human and liver related TZD effects has currently not been investigated, but would provide much needed information on the mechanisms behind the effects of TZD treatment. In addition to providing beneficial effects by inducing adiponectin levels, PPAR $\gamma$  activation also reduces the expression of the inflammatory cytokine TNF $\alpha$  in adipose tissue, which may improve insulin sensitivity by inhibiting TNF $\alpha$ -induced insulin resistance.<sup>15,19</sup>

Thus, activation of PPAR $\gamma$  increases adipose tissue fat storage capacity as well as systemic and local insulin sensitivity. However, these benefits come at the expense of increased adiposity, which in itself may increase the risk of debilitating co-morbidities and reduce patient compliance, collectively supporting the need for refined pharmacological targeting of PPAR $\gamma$ .

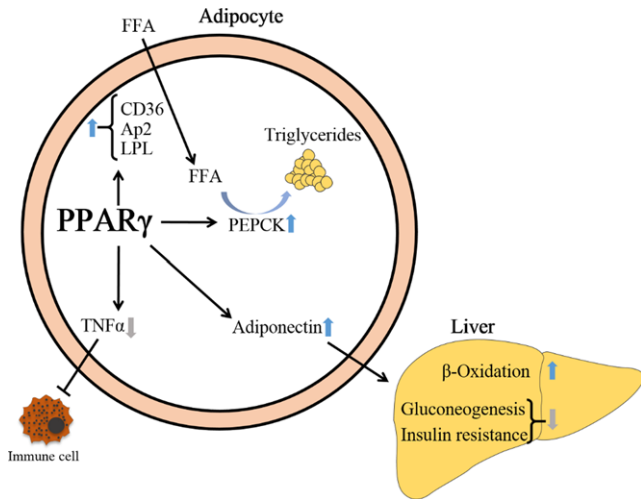
**TABLE 1** Clinical trials investigating the effects of currently approved Thiazolidinediones in non-alcoholic fatty liver disease

| Clinical trial  | Type of trial  | Primary outcome   | Secondary outcomes   | Criteria for enrolment   | Results  |
|---|--|---|--|--|--|
| Rosiglitazone <sup>a</sup> vs placebo<br>FLIRT<br>NCT00492700 <sup>8</sup>  | Randomized, double-blind placebo-controlled<br>(n = 63)  | Improvement in steatosis  | Improvement in ALT/AST levels, improvement/less worsening in necrosis and inflammatory activity and/or fibrosis                  | Biopsy-proven NASH with steatosis $\geq 20\%$  | Improvement in steatosis and insulin sensitivity   |
| Rosiglitazone <sup>a</sup> vs placebo<br>FLIRT2<br>NCT00492700 <sup>7</sup> | Open-label, 2-y extension<br>(n = 44)  | Improvement in steatosis  | Improvement in ALT/AST levels, improvement/less worsening in necrosis and inflammatory activity and/or fibrosis                  | Biopsy-proven NASH with steatosis $\geq 20\%$  | No change in steatosis.<br>Improvement in insulin sensitivity  |
| Pioglitazone vs placebo<br>NCT00227110 <sup>13</sup>                        | Randomized, double-blind placebo-controlled<br>(n = 55)  | Improvement in liver histology                                  | Liver fat content MRS, double-tracer OGTT (EGP, glucose clearance)   | Biopsy-proven NASH must have impaired glucose tolerance or type 2 diabetes                     | Improvement in steatosis and inflammation but not fibrosis   |
| Pioglitazone vs Placebo <sup>b,12</sup>                                     | Randomized, double-blind placebo-controlled<br>(n = 74)  | Reduction in hepatocyte injury and fibrosis scores on histology | Improvement in biochemical and metabolic parameters  | Biopsy-proven NASH   | Improvement in hepatocyte injury, non-significant improvement in fibrosis ( $P = 0.05$ )                   |
| Pioglitazone vs Vitamin E vs placebo<br>PIVENS<br>NCT00063622 <sup>10</sup> | Randomized, double-blind placebo-controlled<br>(n = 247)   | Improved liver histology without worsening of fibrosis          | Improvement in anyone of the following: steatosis, lobular inflammation, hepatocellular ballooning, fibrosis, resolution of NASH | Biopsy-proven NASH, biopsy must be obtained within 6 mo of randomization, must be non-diabetic | Primary outcome for pioglitazone was not met, but secondary outcomes (steatosis and inflammation) were met |
| Pioglitazone vs placebo<br>NCT00994682 <sup>9</sup>                         | Randomized, double-blind placebo-controlled, followed by 18 mo open-label extension<br>(n = 101) | Number of patients with at least 2 point reduction in NAS score | Improvement in individual histological scores  | Prediabetes or type 2 diabetes, and biopsy-proven NASH   | Improvement in NAS score, number of patients with resolution of NASH, and fibrosis score                   |

ALT, Alanine transaminase; AST, Aspartate transaminase; EGP, Endogenous glucose production; MRS, Magnetic resonance spectroscopy; NAS, NAFLD activity score; OGTT, Oral glucose tolerance test.

<sup>a</sup>Only FDA approved.

<sup>b</sup>No ClinicalTrials.gov identifier.



**FIGURE 1** PPAR $\gamma$ -mediated effects in adipocytes. In adipocytes, PPAR $\gamma$  regulates the expression of genes controlling FFA uptake, storage and adipose tissue endocrine function. PPAR $\gamma$  activation leads to increased expression of CD36, Ap2 and LPL which are all involved in the enhanced transport and uptake of free fatty acids across the cell membrane. The increased expression of PEPCK exerts excessive production of triglycerides from the incoming FFAs, leading to intracellular fat deposition. PPAR $\gamma$  also induces increased adiponectin expression, mediating higher amounts of circulating adiponectin and facilitating tissue crosstalk. Circulating adiponectin will bind to receptors in the liver initiating signalling cascades leading to increased  $\beta$ -oxidation, decreased gluconeogenesis and less insulin resistant hepatic tissue. Lastly, the lower TNF $\alpha$  production will prevent recruitment and activation of immune cells, adipose tissue dysfunction and systemic low-grade inflammation. Ap2, Adipocyte Protein 2; CD36, Cluster of Differentiation 36; FFA, Free Fatty Acids; LPL, Lipoprotein Lipase; PEPCK, Phosphoenolpyruvate Carboxykinase; TNF $\alpha$ , Tumour Necrosis Factor  $\alpha$ . Blue arrows: Increase, grey arrows: Decrease

### 3 | PPAR $\gamma$ IN THE LIVER

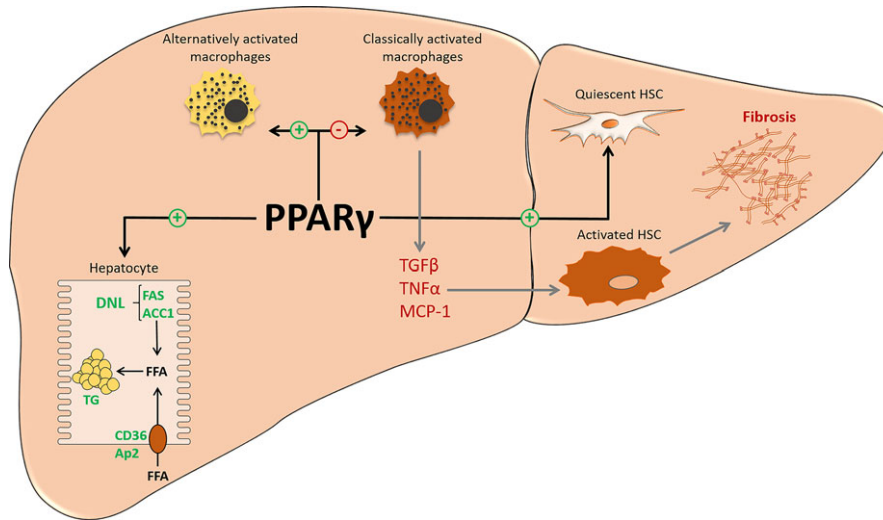
Studies in lipoatrophic AZIP mice have shown that in the absence of adipose tissue, the liver is the primary target of TZDs.<sup>16</sup> In the liver, PPAR $\gamma$  regulates a multitude of processes in hepatocytes, liver resident macrophages (Kupffer cells) and hepatic stellate cells (HSCs).<sup>32–37</sup> The latter two are pivotal in the progression of hepatic inflammation and the development of fibrosis, hence in NAFLD progression and subsequently in determining patient outcome.<sup>2,4</sup> A putative role in disease progression is supported by the finding of increased hepatic PPAR $\gamma$  expression in NAFLD patients, linking PPAR $\gamma$  to the pathogenesis of NAFLD.<sup>38</sup>

#### 3.1 | PPAR $\gamma$ in hepatocytes

In hepatocytes, PPAR $\gamma$  is a regulator of lipid metabolism, targeting genes involved in de novo lipogenesis (DNL) and FFA import (Figure 2). In response to a high-fat diet

(HFD), adipose tissue becomes dysfunctional promoting lipolysis and subsequently hyperlipidaemia.<sup>20</sup> This can cause the liver to act as a secondary reserve for the excess lipid load, inducing the expression of adipogenic genes including PPAR $\gamma$ , mediating an adipogenic transformation of hepatocytes.<sup>39–41</sup> In hepatocytes, PPAR $\gamma$  promotes adipocyte protein 2 and cluster of differentiation 36-mediated FFA uptake and induces the DNL enzymes' fatty acid synthase and acetyl-CoA carboxylase 1, facilitating an increase in hepatic triglycerides (Figure 2).<sup>39,40,42,43</sup> Thus, the hepatic effects of PPAR $\gamma$  appear to be steatogenic, promoting the deposition of intracellular lipids. Indeed, mice with hepatocyte-specific knockout of PPAR $\gamma$  showed a significant reduction in hepatic lipid vacuoles, as well as down-regulation of DNL activators: sterol regulatory element binding protein 1c and acetyl-CoA carboxylase 1, fatty acid importer cluster of differentiation 36 and storage enzyme phosphoenolpyruvate carboxykinase, in response to a HFD compared with wild-type controls (Table 2).<sup>33</sup> Despite reducing hepatic steatosis, hepatocyte-specific PPAR $\gamma$  ablation in lipoatrophic AZIP mice caused a 33% increase in muscle triglyceride content and induced insulin resistance, emphasizing that PPAR $\gamma$  is not only a key factor in hepatic lipid homeostasis, but also exerts significant effects in regulating lipid deposition and cellular metabolism in additional tissues.<sup>16</sup> Furthermore, liver-specific PPAR $\gamma$  knockout in *ob/ob* mice significantly increased serum FFA levels by almost 60%, while reducing liver triglyceride contents compared with control mice.<sup>43</sup> Consequently, decreased hepatic lipid content follows the disruption of hepatocyte PPAR $\gamma$ , but comes at the expense of excess lipid delivery to other tissues, such as striated muscles. This augments insulin resistance (which has been reported in some studies of PPAR $\gamma$  knockout mice<sup>16,43</sup>) and, subsequently, the development of type 2 diabetes, and may undermine an—at first glance beneficial—anti-steatogenic effect of PPAR $\gamma$  inhibition in hepatocytes.

Rosiglitazone treatment in obese *ob/ob* and the obese/diabetic KKA $\gamma$  mouse model (KK mouse strain crossed with mice carrying the yellow obese gene A $\gamma$ <sup>44</sup>) increased hepatic lipid accumulation, again substantiating the steatogenic role of hepatocyte PPAR $\gamma$  agonism.<sup>43,45</sup> In line with these findings, the expected outcome of the increased hepatic PPAR $\gamma$  expression reported for NAFLD patients would be hepatocyte activation of DNL and adipogenic gene expression subsequently resulting in aggravated steatosis.<sup>38,41</sup> Yet, clinical trials show significant reduction of hepatic steatosis in NAFLD patients treated with the PPAR $\gamma$  agonists rosiglitazone and pioglitazone (Table 1).<sup>7–9,46</sup> This alleviation is likely caused by effects in the adipose tissue, where PPAR $\gamma$  activation supports the formation of healthy adipose tissue thereby preventing shunting of excess lipids to the liver and the formation of dysfunctional



**FIGURE 2** PPAR $\gamma$ -mediated effects in the liver. PPAR $\gamma$  serves distinct functions in the various cell types of the liver. In hepatocytes, PPAR $\gamma$  has a steatogenic role, mediating expression of adipogenic genes such as Ap2 and CD36 inducing increased FFA uptake. The simultaneous induction of FAS and ACC1 promotes intracellular TG accumulation. In liver macrophages, both Kupffer cells and infiltrating monocytes, PPAR $\gamma$  promotes the alternatively activated (M2) macrophage phenotype, while inhibiting activation of the classically activated (M1) macrophage. This decreases the release of inflammatory cytokines (EG TNF $\alpha$  and MCP1) and growth factors (TGF $\beta$ ), resulting in reduced inflammation, and hepatic stellate cell activation in turn attenuating fibrosis. Finally, PPAR $\gamma$  is associated with the quiescent phenotype of HSC limiting activation of HSC and subsequently fibrosis. ACC1, Acetyl-CoA Carboxylase 1; Ap2, Adipocyte Protein 2; CD36, Cluster of Differentiation 36; DNL, De Novo Lipogenesis; FAS, Fatty Acid Synthase; FFA, Free Fatty Acid; Green text/“+”, increased; HSC, Hepatic stellate cell; MCP1, Monocyte chemoattractant protein 1 (CCL2); Red text/“-”, decreased; TG, Triglyceride; TGF $\beta$ , Transforming Growth Factor  $\beta$ ; TNF $\alpha$ , Tumour Necrosis Factor  $\alpha$ . Grey arrows: Decreased pathway induction

**TABLE 2** Pre-clinical mouse models of cell-specific PPAR $\gamma$  knockout

| Genotype   | Model of injury  | Altered hepatic gene expression                                     | Liver features                                 | Metabolic features                                     | Compound            | Compound effect  |
|--|------------------|---|--|--|---------------------|--|
| PPAR $\gamma^{\Delta\text{Hep33}}$                             | HFD              | $\beta$ -ox $\downarrow$<br>DNL $\downarrow$<br>Import $\downarrow$ | Steatosis $\downarrow$                         | Improved glucose clearance                             | Rosiglitazone       | Loss of steatogenic effect compared with WT <sup>b</sup>         |
| PPAR $\gamma^{\Delta\text{Hep}}$<br>AZIP <sup>a16</sup>        | None             | Non-significant findings  | Steatosis $\downarrow$                         | Hyperlipidaemia, impaired muscle insulin sensitivity   | Rosiglitazone       | Loss of steatogenic effect compared with AZIP WT                 |
| PPAR $\gamma^{\Delta\text{Hep}}$<br><i>ob/ob</i> <sup>43</sup> | None             | DNL $\downarrow$  | Steatosis $\downarrow$                         | Hyperlipidaemia<br>Impaired muscle insulin sensitivity | Rosiglitazone       | Loss of steatogenic effects compared with <i>ob/ob</i> WT        |
| PPAR $\gamma^{\Delta\text{Mac34}}$                             | CCL <sub>4</sub> | Inflammatory $\uparrow$<br>Fibrotic $\uparrow$                      | Inflammation $\uparrow$<br>Fibrosis $\uparrow$ | ND   | Rosiglitazone + LPS | Increased expression of pro-inflammatory M1 markers <sup>b</sup> |
| PPAR $\gamma^{\Delta\text{HSCc34}}$                            | CCL <sub>4</sub> | Fibrotic $\uparrow$   | Fibrosis $\uparrow$                            | ND   | Rosiglitazone       | ND   |

$\Delta$ : PPAR $\gamma$  deletion in specific cell type; DNL, de novo lipogenesis; Hep, hepatocyte; HFD, high-fat diet; HSC, hepatic stellate cell; IR, insulin resistance; Mac, macrophages; ND, no data; WT, wild-type;  $\beta$ -ox,  $\beta$ -oxidation.

<sup>a</sup>Mice did not develop adipose tissue.

<sup>b</sup>Only tested in precision-cut liver slices and primary hepatocyte cultures.

<sup>c</sup>HSC-specific PPAR $\gamma$  disruption was performed under control of the ap2 promoter, and ap2 is not HSC specific but also expressed in adipocytes<sup>70</sup> and Kupffer cells.

adipocytes.<sup>6,15</sup> An increased formation of adipose tissue is supported by the observed weight gain in TZD-treated NAFLD patients.<sup>7,9,10</sup> Although patients with NAFLD display increased levels of liver PPAR $\gamma$ , the specific events

triggering this up-regulation during disease progression have not yet been identified.<sup>38</sup> PPAR $\gamma$  might be up-regulated in response to lipid accumulation in hepatocytes, or PPAR $\gamma$  could be up-regulated in response to stimuli prior

to the lipid build-up. As PPAR $\gamma$  induces the expression of genes involved in lipid uptake and storage, an up-regulation of PPAR $\gamma$  prior to steatosis could place PPAR $\gamma$  as a causal factor of hepatic lipid accumulation in NAFLD patients. In mice subjected to HFD-induced NAFLD, PPAR $\gamma$  was up-regulated as early as 2 weeks after initiating the dietary regime, preceding development of obesity and insulin resistance.<sup>47</sup> At this time-point, HFD-fed mice had already developed steatosis, but as PPAR $\gamma$  levels were not measured earlier, a time-dependent up-regulation prior to the onset of hepatic histopathological lesions could not be assessed. The finding that adenovirus-induced hepatic PPAR $\gamma$  overexpression led to hepatocyte lipid accumulation (steatosis) even in the absence of a dyslipidaemic diet,<sup>43</sup> supports a link between PPAR $\gamma$  expression and induced liver steatosis.

### 3.2 | PPAR $\gamma$ in liver macrophages and Kupffer cells

In response to a hepatic insult, such as increased lipid load, resident hepatic macrophages (Kupffer cells) are activated (Figure 2). Upon activation, Kupffer cells release inflammatory cytokines leading to the recruitment of additional immune cells, fuelling the inflammatory cascade and NASH progression.<sup>48</sup> Macrophages have been broadly classified as classically activated inflammatory (M1) or alternatively activated anti-inflammatory (M2). M1 macrophages express pro-inflammatory cytokines such as TNF $\alpha$ , interleukin-1 (IL-1 $\beta$ ), IL-8 and metabolize arginine to nitric oxide, which can be further processed into reactive nitrogen species. M2 macrophages express anti-inflammatory cytokines (eg IL-10) and growth factors such as TGF $\beta$  and metabolize arginine to ornithine and urea, providing precursors for amino acid and collagen synthesis important for tissue remodelling.<sup>48,49</sup> A current view on macrophage polarization is more nuanced and suggests a “spectrum model” encompassing a wider range of activation states, reflecting the many different stimuli and subsequent response characteristics.<sup>50,51</sup> However, for the simplicity of this MiniReview, and in relation to the terminology of the papers included, we will refer to the M1 and M2 macrophage states. In morbidly obese patients, markers of liver M2 macrophages were inversely correlated with the degree of liver steatosis, suggesting a “macrophage-switch” away from the anti-inflammatory M2 phenotype as an indicator of NAFLD disease stage, at least in this subgroup of patients.<sup>52</sup> However, the study did not disclose a putative link between M2 markers and degree of hepatic inflammation and fibrosis, leaving the predictive and putative therapeutic potential of the M1:M2 findings to be further explored.

The role of macrophage (including Kupffer cell) polarization in NAFLD has been addressed in studies with

C57Bl/6 mice. This mouse strain does not support the complete maturation of the M2 phenotype, resulting in an enhanced M1 polarization and subsequent increased NASH severity, compared with Balb/c counterparts, which do not exhibit this “M1-bias”.<sup>35,53,54</sup> In Balb/c mice, bone marrow-derived macrophage-specific PPAR $\gamma$  deletion inhibited maturation of M2 macrophages and promoted insulin resistance as well as diet-induced obesity.<sup>35</sup> Furthermore, CCL<sub>4</sub>-induced liver injury caused increased hepatic expression of M1 inflammatory cytokines (TNF $\alpha$  and IL-1 $\beta$ ) and exacerbated fibrosis in mice with Kupffer cell-specific PPAR $\gamma$  deficiency compared with wild-type controls (Table 2).<sup>34</sup> This indicates that loss of macrophage PPAR $\gamma$  induces M1 polarization and enhances liver injury. Conversely, PPAR $\gamma$  activation might improve NAFLD/NASH by negating M1 polarization and the ensuing inflammatory cascade, instead promoting M2 activation (Figure 2). Accordingly, a recent study found that PPAR $\gamma$  induction by rosiglitazone decreased the number of M1 Kupffer cells in the liver, attenuating the inflammatory response as well as steatosis in a diet-induced murine NAFLD model.<sup>32</sup> However, whether rosiglitazone reduced the number of M1 Kupffer cells directly or whether the effect was indirectly mediated through the decreased degree of steatosis was not assessed.

Collectively, these studies suggest a central role of PPAR $\gamma$  in NAFLD-associated hepatic inflammation, by promoting the activation of M2 macrophages while reducing the number of M1 macrophages, thereby, alleviating inflammation and preventing disease progression.

### 3.3 | PPAR $\gamma$ function in hepatic stellate cells

Hepatic stellate cells are characterized by enhanced  $\alpha$  smooth muscle actin, extracellular matrix production and play a central role in the fibrotic deposition in NAFLD.<sup>55</sup> During NAFLD progression, growth factors such as TGF $\beta$  induce HSCs to switch from a PPAR $\gamma$  expressing quiescent phenotype to an activated phenotype with decreased PPAR $\gamma$  expression (Figure 2).<sup>55–57</sup> Activated hepatic stellate cells also produce tissue inhibitors of metalloproteinases (TIMPs), which inhibit matrix degradation, promoting fibrosis.<sup>56</sup>

Pioglitazone treatment prevented hepatic fibrosis and reduced the expression of the pro-fibrotic TIMP-1 and TIMP-2 genes in rats subjected to a NAFLD-inducing, choline-deficient L-amino acid-defined (CDA) diet.<sup>58</sup> In mice subjected to an MCD diet, overexpression of PPAR $\gamma$  reversed hepatic fibrosis and reduced the expression of  $\alpha$  smooth muscle actin, TIMP-1 and TIMP-2 indicating that PPAR $\gamma$  directly reduced liver fibrosis.<sup>37</sup> In line with these findings, HSC-specific ablation of PPAR $\gamma$  aggravated CCL<sub>4</sub>-induced liver fibrosis and increased  $\alpha$  smooth muscle actin expression (Table 2).<sup>34</sup> Collectively, these findings

link increased PPAR $\gamma$  activation/expression to reductions in hepatic fibrosis; however, treatment effectiveness may depend on time of intervention and disease severity. Accordingly, pioglitazone only ameliorated hepatic fibrosis when administered in rats with moderate pericentrilobular fibrosis, whereas treatment had no effect in animals with severe bridging fibrosis.<sup>59</sup> This could be explained by a decrease in PPAR $\gamma$  expression concomitant with HSC activation, reducing TZD effects by diminishing target availability.<sup>57,59</sup> While clinical trials have suggested anti-steatogenic and anti-inflammatory actions of pioglitazone, and to a lesser degree rosiglitazone, the effects on fibrosis have been less clear (Table 1). A recent meta-analysis of TZD effects from eight randomized, controlled trials (n = 516) on NASH-associated liver fibrosis found pioglitazone to significantly improve fibrosis, particularly advanced fibrosis (stage F3-F4 [bridging fibrosis and cirrhosis] to stage F0-F2 [no fibrosis to mild perisinusoidal/periportal fibrosis]), whereas this was not the case for rosiglitazone.<sup>11</sup> TZDs may impose additional effects, for example, by binding alternative targets such as the mitochondrial pyruvate carrier.<sup>60</sup> Inhibition of the mitochondrial pyruvate carrier by a next-generation TZD (MSDC-0602) reversed hepatic fibrosis in vivo in mice with diet-induced NASH, supporting the mitochondria pyruvate carrier as a relevant treatment target.<sup>61</sup> Pioglitazone is generally used at a considerably higher dosage than rosiglitazone (30-45 mg and 4-8 mg, respectively),<sup>8-10,62</sup> and additional target binding could be speculated to be a contributing factor to the superior clinical effect of pioglitazone on NAFLD-associated end-points, compared to other TZDs such as rosiglitazone.<sup>63</sup>

#### 4 | EMERGING STRATEGIES TO TARGET PPAR $\gamma$ IN THE TREATMENT OF NAFLD

Assessing the different roles of PPAR $\gamma$  in the liver has unveiled several potential therapeutic targets. Compounds targeting PPAR $\gamma$  with higher tissue, cell or pathway specificity could reduce side effects (such as the unwanted weight gain reported for TZD treatment) and might prove superior in treating the multifactorial pathogenesis of NAFLD.

In healthy individuals, DNL only contributes to ~5% of the total intrahepatic triglycerides; however, in NAFLD patients, this number increases to 15%-23%, indicating an up-regulation of DNL, and also suggesting that the majority of intrahepatic triglycerides in NAFLD patients originate from reduced secretion and/or increased uptake of free fatty acids.<sup>20,64</sup> The latter is in agreement with increased lipolysis of adipose tissue often seen in individuals suffering from obesity and insulin resistance.<sup>20</sup> PPAR $\gamma$  in

adipose tissue provides an attractive therapeutic target by decreasing FFA release and ameliorating hepatic steatosis indirectly by diminishing hepatic lipid uptake. However, the resulting weight gain—averaging around 2.5 kg in long-term TZD treatment—is a major drawback which potentially reduces compliance and applicability.<sup>9</sup> Assessment of post-translational PPAR $\gamma$  modifications has revealed a cyclin-dependent kinase 5 (Cdk5) as a potential drug-target.<sup>65</sup> Cdk5 is expressed in adipose tissue in response to inflammatory cytokines and a HFD, and phosphorylates Ser273 on PPAR $\gamma$  leading to aberrant gene expression and insulin resistance.<sup>65</sup> Rosiglitazone reduced Cdk5-mediated phosphorylation of PPAR $\gamma$  in obese individuals and mediated an improvement in insulin sensitivity.<sup>65</sup> Compared with rosiglitazone, SR1664, a novel small-molecule compound, blocked Cdk5-induced PPAR $\gamma$  phosphorylation and had anti-diabetic effects, despite showing a limited degree of classical PPAR $\gamma$  agonism, as SR1664 did not promote adipocyte differentiation or expression of adipogenic genes in the investigated mice.<sup>66</sup> Whether Cdk5-mediated phosphorylation affects PPAR $\gamma$ -mediated adipogenic gene expression in hepatocytes has not yet been investigated. However, if this is the case, inhibiting Cdk5-mediated phosphorylation could provide a way to block or limit an unwanted adipogenic aspect of hepatic PPAR $\gamma$  action, without compromising the beneficial effects of PPAR $\gamma$  in HSCs and macrophages.

In contrast to PPAR $\gamma$  which promotes hepatic DNL, other members of the PPAR family, PPAR $\alpha$  and PPAR $\delta$ , induce fatty acid oxidation hereby enhancing lipid catabolism.<sup>6</sup> Exploiting the positive effects of PPAR $\gamma$  while limiting adverse effects by targeting other PPARs has paved the road for the development of a new group of dual and pan agonists, targeting two and three PPARs, respectively. Glitazars constitute a novel group of dual agonists targeting both PPAR $\gamma$  and PPAR $\alpha$ .<sup>6</sup> Of these, saroglitazar has shown promising results in pre-clinical models, reversing CCL<sub>4</sub>-induced hepatic fibrosis and NASH caused by a CDAA diet in mice.<sup>67</sup> Specifically, saroglitazar improved steatosis, hepatocellular ballooning, lobular inflammation and fibrosis (scored collectively) by 78% whereas pioglitazone showed 22% and fenofibrate (a PPAR $\alpha$  agonist) a 54% improvement, all compared with vehicle.<sup>67</sup> Saroglitazar is currently approved for the treatment of diabetic hypertriglyceridaemia and dyslipidaemia in India,<sup>67,68</sup> and a phase 3 clinical trial comparing saroglitazar and pioglitazone treatment in NAFLD patients is currently ongoing (ClinicalTrials.gov identifier: NCT02265276). The pan agonist IVA337 has recently shown promising results by improving NASH histology and the expression of inflammatory cytokines in both obese *foz/foz* mice and in mice fed a MCD diet, as well as reducing weight gain and normalizing plasma glucose and insulin levels in a mouse model of diet-induced



obesity.<sup>69</sup> Furthermore, IVA337 prevented and reversed CCl<sub>4</sub>-induced liver fibrosis more effectively than any of the single agonists fenofibrate (PPAR $\alpha$ ), GW501516 (PPAR $\delta$ ) and rosiglitazone (PPAR $\gamma$ ).<sup>69</sup> Currently, investigators are recruiting patients with more than 10% intrahepatic triglycerides for a phase 2 trial (ClinicalTrials.gov identifier: NCT03459079), and patients with histologically proven NASH for a phase 2b trial testing IVA337 (ClinicalTrials.gov identifier: NCT03008070). These results support the use of dual and pan agonists as the future PPAR-targeting treatment in NAFLD, although their efficacy in humans remains to be confirmed in randomized, controlled clinical trials.

## 5 | CONCLUDING REMARKS

Despite the identification of PPAR $\gamma$  almost 25 years ago, the search for new and more specific ways of targeting this nuclear receptor continues and may prove valuable in future treatment strategies for NAFLD and NASH patients. PPAR $\gamma$  exerts distinct functions in the liver, and while PPAR $\gamma$  activation in HSCs and macrophages seems beneficial in protecting against NAFLD and NASH promotion, the opposite is true for hepatocytes. In vitro studies have discovered cell- and tissue-specific post-translational modifications of PPAR $\gamma$ , suggesting that PPAR $\gamma$ -mediated undesirable side effects may be reduced through specific treatment targets. An improved overall outcome could also be achieved by targeting more than one PPAR subtype, that is dual or pan agonists, hereby optimizing beneficial effects. Thus, though NAFLD/NASH and associated hepatic fibrosis is the result of a complex and yet undisclosed causal interaction between multiple factors, PPARs appear to play a central role in the propagation of disease, with PPAR $\gamma$  currently taking the lead as a pivotal factor in driving or diminishing hepatic damage. The ability to selectively balance beneficial and undesirable effects will determine their future therapeutic potential in NAFLD.

## CONFLICT OF INTEREST

The authors declare no conflict of interest that could influence this work.

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