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REVIEW

Therapeutic Targeting of PPARγ in Nonalcoholic Fatty Liver Disease: Efficacy, Safety, and Drug Development

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Abstract: Non-alcoholic fatty liver disease (NAFLD) is a metabolic-associated liver disorder characterized by a multi-faceted pathological progression involving fat accumulation, oxidative stress, and inflammation. Peroxisome proliferator-activated receptor gamma (PPARγ), a key nuclear receptor involved in lipid metabolism, insulin sensitivity regulation, and immune modulation, plays a significant role in both the development and treatment of NAFLD. This review summarizes the physiological functions of PPARγ in tissues such as adipose tissue, pancreas, intestine, and liver. Furthermore, it compiles current clinical research progress on PPARγ agonists, including mono-agonists, dual agonists, and pan-agonists, and analyzes their associated side effects, mechanisms of occurrence, and potential solutions. Importantly, therapeutic strategies targeting PPARγ hold promise for improving steatosis and insulin resistance and inhibiting liver fibrosis. Future research is needed to further explore the influence of blood insulin levels, hepatic PPARγ levels, and tissue-specific factors on the therapeutic efficacy of PPARγ agonists. Besides, the development of novel PPAR multi-agonists, partial PPARγ agonists, and combination therapies should be explored to optimize therapeutic outcomes while minimizing adverse effects, thereby providing new directions for precision medical interventions in NAFLD.

Keywords: PPARγ, NAFLD, therapeutic efficacy, adverse effects

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is characterized by the abnormal accumulation of fat in the liver, excluding alcoholic causes. It is defined by the presence of fat in more than 5% of hepatocytes or fat accounting for more than 5% of the liver's total weight.[1] NAFLD encompasses simple steatosis and non-alcoholic steatohepatitis (NASH).[2] Due to the widespread adoption of Westernized lifestyles and the slow progression of the disease, NAFLD is recognized as the most common chronic liver disease globally, affecting approximately 38% of the adult population.[3,4] Furthermore, NAFLD is associated with a variety of adverse outcomes, including cirrhosis, liver failure, hepatocellular carcinoma, and extrahepatic conditions such as cardiovascular disease, type 2 diabetes, chronic kidney disease, and certain extrahepatic cancers.[2,4] Intervening to halt the progressive accumulation of simple hepatic steatosis and preventing its advancement to NASH, cirrhosis, carcinogenesis, and other detrimental outcomes is of significant importance for improving human health.

The initial pathogenesis of NAFLD was described by the "two-hit" hypothesis, which proposed that hepatic steatosis (first hit) predisposes the liver to subsequent damage caused by oxidative stress and inflammation (second hit). However, this model has been largely replaced by the "multiple-hit" hypothesis, which better reflects the interplay of various metabolic, environmental, and genetic factors. In this model, insulin resistance plays a central role by promoting increased lipolysis in adipose tissue, elevating free fatty acid flux to the liver, and enhancing de novo lipogenesis, thereby triggering lipotoxicity,

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promoting oxidative stress, and initiating the activation of inflammatory cascades.[5] Adipokines such as adiponectin, leptin, and resistin, secreted from dysfunctional adipose tissue, further exacerbate inflammation and metabolic dysregulation. Additionally, dysbiosis of the gut microbiota contributes to increased intestinal permeability and endotoxin-mediated hepatic inflammation. Genetic polymorphisms, such as those in the PNPLA3 and TM6SF2 genes, also influence susceptibility to NAFLD and its progression to NASH and fibrosis.[6] Moreover, adipokines, gut microbiota, and genetic polymorphisms contribute to NAFLD, in part by disrupting insulin signaling cascades.[5]

A healthy diet and regular physical activity remain the most fundamental and reliable strategies for the treatment of NAFLD. Several drugs approved for other indications have shown potential benefits for NAFLD in clinical trials, including vitamin E, thiazolidinediones (TZDs), glucagon-like peptide-1 receptor agonists (GLP-1RAs), and sodium-glucose cotransporter-2 (SGLT-2) inhibitors.[7] All of these agents have demonstrated efficacy in reducing hepatic steatosis; however, only TZDs have been proven to improve liver fibrosis to date.[8] Nevertheless, due to varying degrees of potential side effects and insufficient clinical validation of their efficacy in treating NAFLD, none of these drugs have yet been approved by the FDA specifically for NAFLD treatment.

Our focus is on thiazolidinediones (TZDs), a class of drugs that includes rosiglitazone and pioglitazone, which were approved by the FDA on May 25 and July 15, 1999, respectively. Originally developed for the treatment of type 2 diabetes, these agents improve insulin sensitivity and have since been investigated for their potential benefits in NAFLD.[9,10] And TZDs are assumed to enhance insulin sensitivity by modulating the Peroxisome Proliferator-Activated Receptors (PPARs) family.

PPARs are ligand-activated nuclear transcription factors that are primarily involved in cellular energy balance, particularly lipid metabolism. PPARα is primarily expressed in the liver and brown adipose tissue, where it plays a central role in fatty acid oxidation. And it is a key target for fibrates, which are used to lower blood lipids. Although PPARα is highly expressed in the liver and is downregulated in patients with NAFLD, fibrates have not demonstrated significant therapeutic effects on NAFLD.[11] PPARβ/δ is widely distributed across various tissues and primarily regulates lipid oxidation to maintain energy homeostasis. However, its activation has been shown to accelerate intestinal adenoma growth and is associated with multiple other tumors, significantly limiting the development of its agonists.[12,13] PPARγ is also widely distributed across various tissues, with high expression in white adipose tissue, playing a crucial role in adipogenesis, insulin sensitivity, and glucose metabolism.

Compared to PPARα and PPARβ/δ, PPARγ has garnered more attention and research for its role in enhancing insulin sensitivity in recent years. Actually, TZDs are considered as classic PPARγ ligands. Beyond improving insulin resistance, PPARγ is a key regulator of lipid metabolism and has demonstrated significant anti-inflammatory effects. Therefore, within both the two-hit and multiple-hit hypotheses, PPARγ remains a highly promising potential therapeutic target for the treatment of NAFLD.

However, PPARγ agonists, despite their efficacy, have limited clinical use due to observed side effects in clinical studies. Rosiglitazone faced restrictions in 2010 for cardiovascular risks, while pioglitazone's use was cautioned against in patients with active bladder cancer following 2011 updates. Notably, rosiglitazone's restrictions were lifted in 2015 after further cardiovascular safety review.

The balance between the usability and potential adverse effects of PPARγ agonists in NAFLD warrants discussion. The role of PPARγ in NAFLD has become controversial. While some pharmacological studies suggest an association between PPARγ and NAFLD progression, others argue that PPARγ activation ameliorates the disease. Given these conflicting findings regarding the effects of PPARγ activation on NAFLD, coupled with the potential side effects of its agonists, the development and clinical application of PPARγ agonists in NAFLD presents significant challenges. Therefore, this article provides a comprehensive review of the usability, safety, and potential developmental directions of PPARγ in NAFLD.[5]

The Role of PPARγ Across Tissues in NAFLD

PPARγ is a member of the peroxisome proliferator-activated receptor family within the nuclear receptor superfamily. Like other family members, it comprises four core structural domains: the N-terminal A/B domain (AF1, ligand-independent activation domain), the C domain (DBD, DNA-binding domain), the D domain (hinge region), and the E/F domain (LBD, ligand-binding domain, which contains AF2, the ligand-dependent activation domain).[14,15] PPARγ's function primarily relies on its two ligand-binding domains. AF1, the ligand-independent domain, partially activates the overall structure by recruiting transcriptional coactivators and can be modulated by other signaling pathways to adjust its activity. AF2, the ligand-dependent domain, is exposed when the LBD binds to ligands (such as fatty acids or TZDs), enabling it to interact with transcriptional coactivators. Activation of either AF1 or AF2 facilitates the formation of a heterodimer between PPARγ and the retinoid X receptor (RXR), allowing the DBD to bind to peroxisome proliferator response elements (PPREs) and drive transcriptional activity. PPARγ has long been thought to be predominantly expressed in adipose tissue, activated mainly by polyunsaturated fatty acids, and closely associated with lipid metabolism. However, its expression has recently been documented in various tissues, including the liver, heart, and kidneys, in different isoforms.[16–18] At the mRNA level, PPARγ exists in four isoforms: γ1, γ2, γ3, and γ4. PPARγ1 mRNA is widely expressed in various tissues, PPARγ2 mRNA is predominantly found in adipose tissue, PPARγ3 mRNA is mainly detected in the intestines and immune cells, and PPARγ4 mRNA has not been fully characterized. It is now understood that PPARγ1, γ3, and γ4 mRNAs encode the PPARγ1 protein, while PPARγ2 mRNA encodes the PPARγ2 protein (Figure 1). The PPARγ2 protein contains an additional 30-amino acid sequence at the N-terminus compared to PPARγ1, endowing it with stronger anti-proliferative, pro-adipogenic, thermogenic, and insulin resistance-improving properties.[14,15,19,20] As a key transcription factor regulating lipid metabolism, PPARγ is broadly distributed and functionally diverse. Therefore, its role in NAFLD is next explored by examining its activities in different tissues.

Liver Tissue

Increasing Fat Uptake and Synthesis

As mentioned above, the PPARγ1 isoform is widely expressed in various tissues, whereas PPARγ2 is predominantly found in adipose tissue. In hepatocytes, PPARγ1 is expressed at higher levels.[21] However, under conditions of high glucose, free fatty acids (FFA), and elevated insulin, hepatocytes exhibit a marked upregulation of PPARγ2 while changes in PPARγ1 are relatively modest.[21,22] This suggests that PPARγ2 may play a more critical role in hepatic lipid

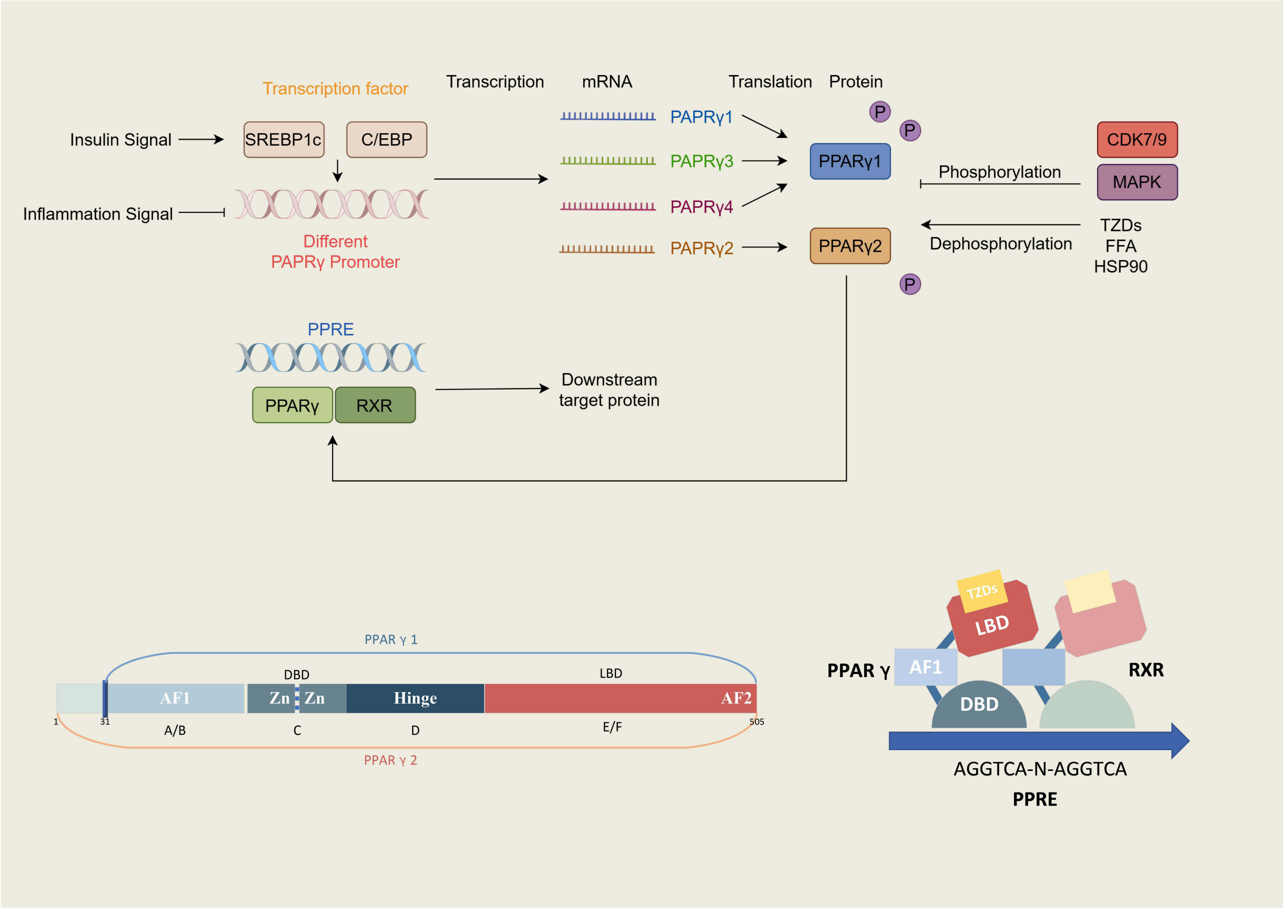

Figure 1 PPARγ expression and activation.

accumulation, even though current studies indicate that both isoforms participate in lipid deposition rather than one acting independently.

Fat deposition in the liver involves increased fat transport and synthesis, coupled with reduced breakdown and β-oxidation. Pharmacological studies have shown that downregulation of PPARγ leads to reduced liver weight and steatosis.[23,24]

Exogenous fatty acids represent the primary source of cellular lipids. The increased uptake of FFAs by hepatocytes can be considered the initiating event in lipid accumulation. PPARγ primarily facilitates this process by directly inducing the transcription of cluster of differentiation 36 (CD36).[21] As a fatty acid transporter, the upregulation of CD36 enhances the binding and uptake of FFAs at the hepatocyte surface, thereby increasing the total intracellular fatty acid content. Moreover, the elevated fatty acid levels subsequently activate SREBP1 and PPARγ-mediated de novo lipogenesis (DNL) sequentially.[25]

The pro-lipogenic influence of PPARγ is largely attributable to its transcriptional regulation of genes involved in lipid synthesis, notably fatty acid synthase (FASN) and fatty acid-binding protein 4 (FABP4).[26,27] Multiple studies have observed that the deletion of PPARγ leads to a downregulation of DNL-related proteins.[28] FASN, a key rate-limiting enzyme in DNL, catalyzes the condensation of acetyl-CoA and seven malonyl-CoA molecules to produce palmitic acid (PA). Excessive production of PA directly contributes to lipid accumulation within hepatocytes. Moreover, PA promotes the activation of NFκB in hepatocytes, thereby inducing oxidative stress, inflammation, and pyroptosis, which exacerbates hepatocellular injury and drives the progression of NASH.[29] Notably, as a long-chain fatty acid, PA also serves as a potent endogenous ligand for PPARγ, further enhancing PPARγ-mediated transcriptional activity, including that of FASN. Interestingly, PPARγ activity is paradoxically suppressed in the context of PA accumulation.[30] This may be attributed to PA-induced oxidative stress and inflammation, in which the strong activation of NFκB exerts a dominant inhibitory effect on PPARγ, overriding its activation by PA. This mechanism also explains the observed downregulation of FASN in hepatocytes during the NASH stage.[31]

Increasing Fatty Acid β-Oxidation, Improving Mitochondrial Function, and Reducing Inflammation

Some pharmacological investigations suggest that PPARγ upregulation is associated with a reduction in NAFLD steatosis, enhanced mitochondrial function, and decreased inflammation.[32,33] As a broad transcription factor, PPARγ influences both lipogenesis and fatty acid oxidation pathways (Figure 2). Its correlation with reduced liver fat is likely due to its capacity to stimulate lipolysis and β-oxidation. Studies have confirmed that PPARγ can reduce hepatic steatosis by promoting mitochondrial fatty acid oxidation.[33] Key enzymes in lipolysis, such as adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL), are activated by PPARγ transcription, promoting the breakdown of triglycerides (TAG) into free fatty acids.[34,35] PPARγ knockdown results in a significant reduction in ATGL, HSL, and CPT1 levels, indicating its regulatory role in lipid synthesis, transport, lipolysis, and fatty acid β-oxidation.

PPARγ inhibits chronic inflammation in hepatocytes through the following multiple mechanisms.

1. Direct inhibition of NF-κB levels in hepatocytes:[36,37] The anti-inflammatory effects of PPARγ primarily stem from its inhibition of the NF-κB pathway. On one hand, PPARγ suppresses the activity of IκB kinase (IKK), reducing the phosphorylation and degradation of IκBα, thereby preventing NF-κB activation and nuclear translocation.[38] On the other hand, PPARγ interacts with the p65 subunit of NF-κB, blocking its binding to target gene promoters.[39] Additionally, PPARγ competes with NF-κB for coactivators, and upon activation, PPARγ preferentially binds more coactivators, thereby reducing their availability for NF-κB.[40] PPARγ also functions as an E3 ligase, directly binding to p65 and inducing its ubiquitination and degradation.[41] Accordingly, NF-κB also inhibits PPARγ expression and activity through multiple mechanisms, including competition for coactivators, direct binding to the PPARγ promoter, and inflammation-induced activation of the ERK signaling pathway, which facilitates PPARγ phosphorylation and functional suppression.[42,43]
2. Enhancement of Nrf2/HO-1 signaling:[44] The nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway represents another crucial mechanism through which PPARγ exerts its anti-inflammatory and antioxidant effects in hepatocytes. PPARγ activation significantly enhances Nrf2 expression at both transcriptional and translational

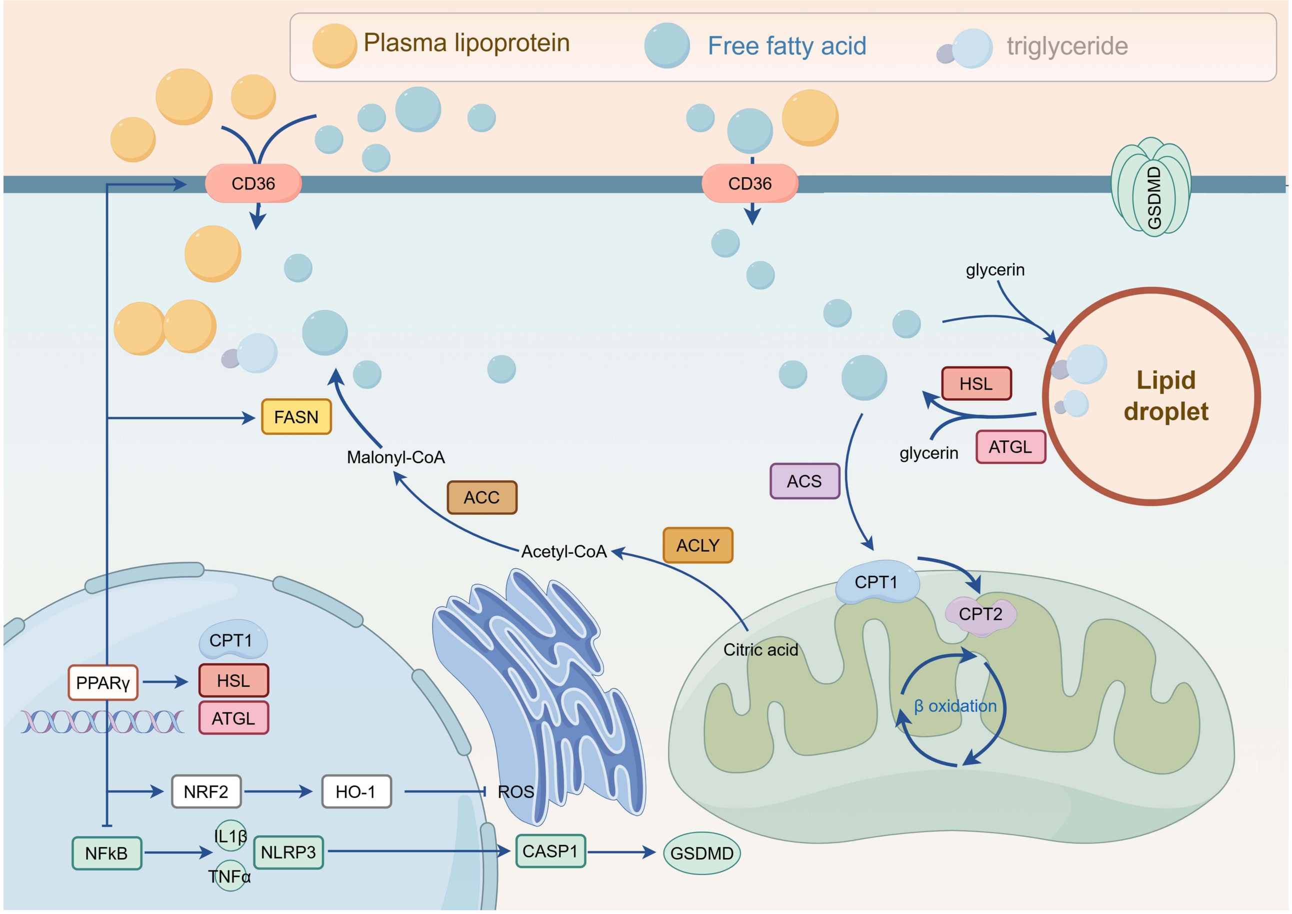

Figure 2 The role of PPARγ in liver.

levels, as evidenced by increased mRNA and protein expression of Nrf2 following treatment with PPARγ agonists.[45] Mechanistically, PPARγ-mediated suppression of the NF-κB/TNF-α/Keap1 pathway promotes the liberation of Nrf2 from its inhibitory Keap1 complex, facilitating Nrf2 nuclear translocation. Upon entering the nucleus, Nrf2 activates the transcription of downstream antioxidant genes, including heme oxygenase-1 (HO-1).[44] HO-1 breaks down heme into carbon monoxide (CO), biliverdin, and iron ions, which exert anti-inflammatory and antioxidant effects by scavenging reactive oxygen species (ROS) and further suppressing NF-κB signaling.[46]

3. Inhibition of inflammasome 3 (NLRP3) activation, reducing pyroptosis:[47] NF-κB serves as the primary transcription factor for NLRP3, and PPARγ inhibits NF-κB activity, thereby reducing the transcription of key pyroptosis-related signals, including NLRP3, ASC, IL-1β, and caspase-1. Additionally, PPARγ activates the Nrf2/HO-1 antioxidant pathway, lowering intracellular ROS levels and suppressing the secondary pyroptosis signal. Furthermore, the DNA-binding domain (DBD) of PPARγ interacts with the nucleotide-binding domain (NBD) and leucine-rich repeat domain (LRR) of NLRP3, preventing the assembly of the NLRP3-ASC inflammasome and ultimately blocking further pyroptotic progression.[48] PPARγ exerts hepatoprotective effects by suppressing pyroptosis in both hepatocytes and hepatic immune cells, thereby alleviating liver injury and preventing cytokine storm through inhibition of excessive inflammatory responses.
4. Activation of hepatocyte growth factor (HGF):[49] Activation of PPARγ in interstitial cells can mediate the transcriptional upregulation of hepatocyte growth factor (HGF). In addition to promoting hepatocyte proliferation and mitigating liver injury, this mechanism recruits anti-inflammatory factors such as HO-1 to suppress immune cell infiltration and inflammatory responses. Furthermore, it inhibits TGF-β signaling to counteract fibrogenesis.[50]

5. Enhancement of autophagy signals within hepatocytes:[51] Activation of PPARγ has been found to upregulate autophagy markers in hepatocytes. This pro-autophagic effect is mediated through activation of AMPK signaling and inhibition of the mTOR pathway.[52,53] Enhanced hepatocyte autophagy further promotes lipophagy (lipid droplet degradation), thereby reducing oxidative stress and alleviating inflammatory responses.
6. Upregulation of circadian rhythm components like Bmal1:[54,55] Rosiglitazone has been found to restore the downregulation of Bmal1 and other clock genes in the liver induced by a high-fat diet. Activation of PPARγ upregulates the expression of the amino acid transporter SLC1A5, enhancing the uptake of glutamine and methionine. These amino acids are further metabolized into acetyl-CoA and S-adenosylmethionine (SAM), which promote histone acetylation and methylation, thereby increasing the activity of the Bmal1 promoter region.[56] The upregulation of clock genes helps correct intracellular circadian rhythm disruptions, breaking the vicious cycle of inflammation and lipid accumulation.
7. Lowering macrophage migration inhibitory factor (MIF) levels in hepatocytes:[57] MIF plays a crucial role in metabolic inflammation. It is expressed in various hepatic cell types, including macrophages and hepatocytes. Upon interacting with its receptor CD74, MIF triggers intracellular signaling cascades such as the MAPK and NF-κB pathways, thereby amplifying the inflammatory response. Activation of PPARγ, however, markedly downregulates MIF expression in hepatocytes, which in turn attenuates the activation of pro-inflammatory pathways like NF-κB and contributes to its anti-inflammatory effects.[58]

Moreover, PPARγ increases the expression of the bile salt export pump (BSEP) in liver tissue, promoting bile acid secretion and preventing liver damage from bile acid retention.[59] PPARγ also indirectly inhibits fibrosis by reducing inflammation-induced damage to liver parenchyma and activation of hepatic stellate cells.[60] PPARγ can inhibit the activation of quiescent hepatic stellate cells by suppressing the signaling of PDGF, EGF, and TGF-β.[61–63] It also remodels the extracellular matrix to combat fibrosis by regulating matrix metalloproteinases (MMPs), such as MMP-2 and MMP-9. Besides, PPARγ increases the release of VEGF from hepatic macrophages, stimulating the proliferation of hepatocytes and promoting liver function recovery.[64]

Adipose Tissue

Adipose tissue serves as the counterpart of the liver-adipose metabolic axis. Adipose tissue is the primary energy storage organ in the human body and the most significant site for fat storage. It regulates lipid homeostasis through the storage and release of lipids, maintaining the balance of the internal environment.[65] Therefore, the functional state of adipose tissue is closely linked to the development and progression of NAFLD. Based on functional and morphological differences, adipose tissue is classified into white adipose tissue (WAT), which stores fat, and brown adipose tissue (BAT), which oxidizes fat to generate heat. White adipose tissue can be further subdivided into subcutaneous white adipose tissue (SAT) and visceral white adipose tissue (VAT) based on its distribution. Among these, visceral white adipose tissue, particularly mesenteric and omental adipose tissue, has the strongest association with NAFLD development due to its anatomical proximity to the liver.[65] As a key regulator of lipid metabolism, PPARγ plays a crucial role in adipocyte differentiation, lipid storage in white adipocytes, and the thermogenic function of brown adipocytes.

Adipocyte Maturation and Differentiation

PPARγ is a critical factor in the maturation and differentiation of adipocytes, acting as both a fundamental and decisive component for adipogenesis.[66] Mature adipocytes, being highly differentiated, cannot undergo mitosis. The formation and renewal of adipose tissue depend on the differentiation of pluripotent stem cells into preadipocytes and their subsequent maturation. Recent studies have shown that certain non-precursor cells, such as fibroblasts and myocytes, can be induced to differentiate into adipocytes through ectopic expression of PPARγ.[67] During adipocyte differentiation and maturation, the CCAAT/enhancer-binding protein (C/EBP) family/PPARγ pathway plays a crucial role. Adipocyte development can be broadly divided into five stages: mesenchymal stem cell, preadipocyte, induced preadipocyte, differentiating adipocyte, and mature adipocyte. During the preparatory phase, precursor cells exit the proliferative cycle and enter G0 phase, marking the transition toward differentiation readiness. In the initiation phase, signals such as insulin and dexamethasone induce the early expression of transcription factors C/EBPβ and C/EBPδ.[68] These are followed by the upregulation of C/EBPα and PPARγ, two master regulators of adipogenesis, PPARγ and C/EBPs engage in a positive feedback loop, mutually reinforcing each other's expression.[69,70] PPARγ, in heterodimerization with RXRα, activates the transcription of adipocyte-specific genes such as aP2 (FABP4), adiponectin, lipoprotein lipase (LPL), and GLUT4, which are involved in lipid synthesis, storage, and insulin sensitivity.[68] This gene activation cascade culminates in the formation of fully differentiated, functionally mature adipocytes. In summary, PPARγ drives the transition from induced preadipocytes to differentiating adipocytes, while the C/EBPα–PPARγ positive feedback loop reinforces and maintains the adipocyte phenotype, ultimately establishing the mature adipocyte identity. In mouse models with PPARγ deficiency, abnormal levels of both PPARγ1 and PPARγ2 result in severely impaired or absent development of WAT and BAT.[71] Besides, conditional knockout of PPARγ in adipose tissue of one-month-old mice leads to chromatin condensation, mitochondrial swelling, reduced mitochondrial function, and progressive adipocyte death.[72] While the loss of PPARγ-mediated adipocyte death is compensated by the replenishment of new adipocytes, the depletion of precursor cell pools with aging results in a decline in the number of mature adipocytes, leading to compensatory hypertrophy of remaining adipocytes, which in turn increases the release of inflammatory signals such as TNFα, IL-1β, and TGF-β (Figure 3). Ultimately, these changes contribute to systemic lipid metabolism disorders and insulin resistance.[73,74]

Promoting Fat Storage in Adipocytes

In addition to its role in adipocyte maturation and differentiation, PPARγ, as a nuclear transcription factor, promotes fat storage in adipocytes by regulating lipid transport and synthesis pathways. PPARγ binds to PPREs, enhancing the expression of lipid transport proteins such as CD36 and FABP4, as well as lipid synthesis proteins like GPDH and ACS. This mechanism increases lipid uptake and storage from the extracellular environment by adipocytes.[75,76]

Endocrine Modulation of Adipocytes

The role of adipokines in maintaining metabolic homeostasis has gained increasing attention in recent years. Among these adipokines, reduced levels of adiponectin are closely associated with the development of metabolic diseases.[77] Adiponectin receptors (AdipoRs) are widely expressed across various tissues, where they enhance cellular insulin sensitivity and fatty acid β-oxidation and reduce inflammation and gluconeogenesis, thus maintaining normal metabolic

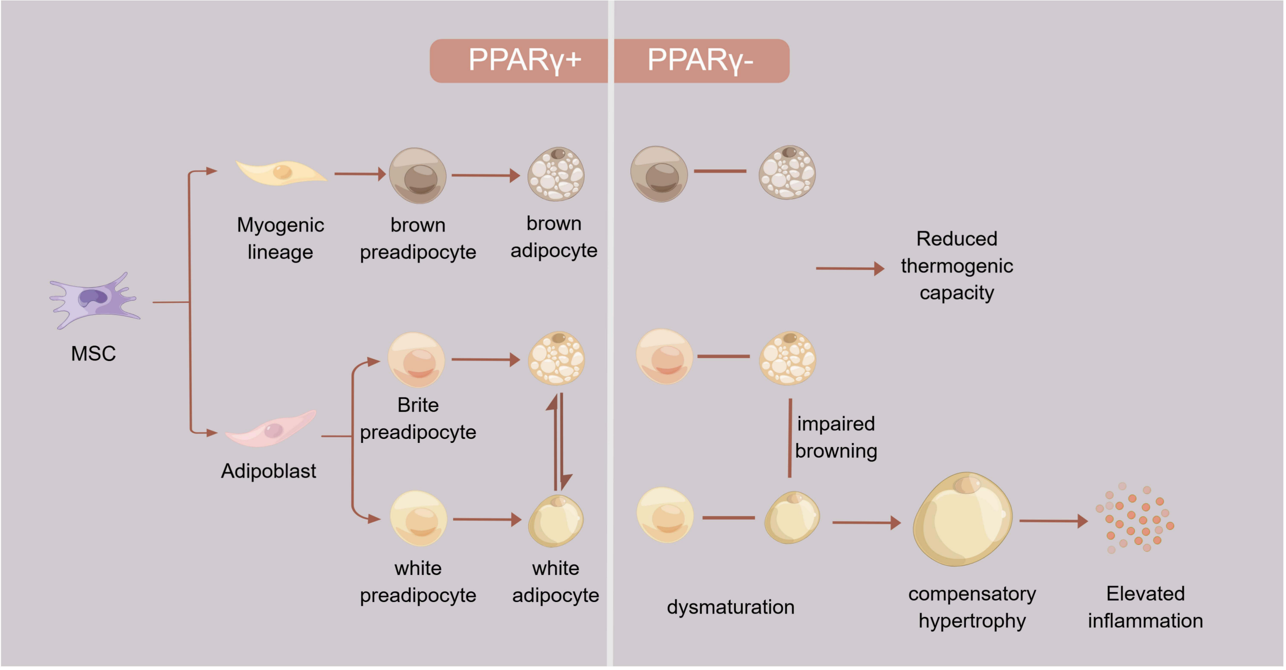

Figure 3 The role of PPARγ in adipocytes.

states.[78,79] A reciprocal regulatory relationship exists between PPARγ and adiponectin. On one hand, PPARγ binds to the adiponectin promoter to stimulate its expression. Studies have demonstrated that the knockout of PPARγ in adipose tissue reduces adiponectin gene expression both within adipocytes and in the systemic circulation.[80] Furthermore, PPARγ activation promotes the formation of adiponectin in its high-molecular-weight (HMW) form, which is the most biologically active configuration, thereby enhancing its effects on target cells and tissues.[81–83] On the other hand, adiponectin can activate PPARγ mRNA and protein expression, with some of its anti-inflammatory and pro-lipid oxidation effects being PPARγ-dependent.[84] Another crucial adipokine, leptin, exhibits a dual and complex role in NAFLD pathogenesis. During early NAFLD stages, leptin appears to ameliorate hepatic lipid accumulation; however, as the disease progresses, it paradoxically promotes inflammation and fibrosis.[85] PPARγ agonists have been shown to reduce leptin levels both in diabetic patients and in in vivo/in vitro obesity models. Conversely, leptin itself has been reported to downregulate PPARγ expression in both adipose and hepatic tissues.[86] Therefore, the activation of PPARγ in adipose tissue, by reducing leptin secretion from adipocytes and lowering serum leptin levels, plays a positive role—at least—in preventing the progression from.

Regulating Mitochondrial Quantity and Function in Adipocytes

Recent studies suggest that brown and white adipocytes originate from distinct precursor cell populations. Current evidence indicates that brown adipocytes may arise from myoblasts, a lineage distinct from that of white adipocytes. This difference in cellular origin may account for the expression of PGC-1α in brown adipocytes, where it interacts with PPARγ to drive the expression of UCP-1. In contrast, white adipocytes typically lack PGC-1α and are considered incapable of expressing UCP-1 under normal conditions.[87] However, under specific stimuli, white adipocytes can acquire the ability to express UCP-1 and exhibit characteristics of brown adipocytes, a phenomenon referred to as "browning". Adipocytes undergoing this transition are termed beige adipocytes. PPARγ is thought to play a central role in regulating UCP-1 expression in adipocytes, increasing the mitochondrial quantity and fatty acid consumption in brown adipocytes,[88] and remodeling the morphology and function of white adipocytes to promote their transformation into beige adipocytes. Furthermore, post-translational modifications of PPARγ significantly influence the browning process of WAT. For instance, deacetylation of PPARγ at lysine residues 268 and 293 (Lys268 and Lys293) promotes WAT browning, increases energy expenditure, and mitigates obesity.[56,89] Conversely, acetylation at these sites upregulates adipsin, destabilizes BMAL1, disrupts the circadian metabolic rhythm of WAT, and contributes to obesity.[56,89] Beyond acetylation, other post-translational modifications of PPARγ, including phosphorylation, ubiquitination, and S-nitrosylation, play critical roles in regulating adipose tissue function.[67]

PPARγ in adipose tissue is widely recognized to play a protective role in maintaining normal adipose tissue function and influencing the development of NAFLD. PPARγ promotes lipid storage in white adipocytes and enhances lipid consumption in brown adipocytes, thereby reducing serum free fatty acid levels. It also regulates the release of adipokines such as leptin and adiponectin, while modulating the release of pro-inflammatory adipokines like TNF-α and IL-1β, thus maintaining a healthy metabolic microenvironment.

Pancreatic Tissue and Insulin Signaling

Maintaining Insulin Secretion

Insulin signaling is pivotal for regulating energy metabolism and preventing metabolic disorders. PPARγ is one of the few known factors with well-established insulin-sensitizing effects, serving as a central mediator in systemic insulin signaling. It supports β-cell survival and enhances insulin secretion.[90] Downregulation of PPARγ leads to a significant reduction in pancreatic β-cell proliferation, proinsulin synthesis, and insulin release. These effects can be reversed by PPARγ agonists, such as rosiglitazone, highlighting the essential role of PPARγ in the initiation of insulin signaling.[91,92] PPARγ promotes insulin synthesis in β-cells by upregulating the expression of pancreatic and duodenal homeobox 1 (PDX-1), a key transcription factor, and upregulating the expression of the insulin gene (*INS*), thereby stimulating proinsulin production.[93,94] Besides, PPARγ regulates β-cell glucose responsiveness to facilitate insulin secretion. It increases the expression of GLUT2, enhancing glucose uptake in β-cells, which is the initial step in glucose-stimulated insulin release. PPARγ also upregulates glucokinase (GCK), promoting the conversion of glucose to ATP. This process activates ATP-dependent K^+ channels, leading to membrane depolarization, the opening of voltage-gated Ca^{2+} channels, and a subsequent rise in intracellular Ca^{2+} levels, which triggers insulin exocytosis.[95,96] Furthermore, PPARγ directly regulates the transcription of SERCA2, which pumps excess Ca^{2+} into the endoplasmic reticulum, maintaining intracellular Ca^{2+} levels in β-cells and ensuring their responsiveness to subsequent glucose signaling.[97]

Enhancing Insulin Sensitivity in Target Organs

In metabolic diseases, reduced insulin sensitivity in target tissues/organs is more commonly observed than insufficient insulin secretion. Insulin resistance arises through two primary mechanisms: impaired insulin signal reception and defective insulin signal execution. Single-gene mutations in PPARγ, AKT2, or the insulin receptor (IRS) can lead to insulin resistance.[98] PPARγ plays a pivotal role in both insulin signal reception and execution by regulating the expression and phosphorylation of IRS and AKT. Specifically, PPARγ inhibits serine (Ser) phosphorylation of IRS-1, thereby increasing the availability of tyrosine phosphorylation sites on IRS-1.[99] This enhances the sensitivity of IRS-1 to insulin signaling, ensuring proper activation of downstream pathways such as PI3K/AKT.[100] Moreover, PPARγ promotes the phosphorylation of AKT at Ser 473, enhancing its activity and leading to increased expression of GLUT4, which facilitates cellular glucose uptake.[100] PPARγ also reduces intracellular levels of reactive oxygen species (ROS) and malondialdehyde (MDA), while increasing superoxide dismutase (SOD) activity and NRF2 expression to maintain redox homeostasis. Furthermore, PPARγ inhibits the transcription of inflammatory factors, thereby preventing insulin resistance.[101] Interestingly, insulin can indirectly upregulate PPARγ expression by activating pathways such as mTOR and PI3K/AKT,[102,103] suggesting a positive feedback loop between PPARγ and insulin signaling that supports energy metabolism balance (Figure 4).

Insulin signaling is vital for maintaining metabolic homeostasis. PPARγ contributes to the proper transmission of insulin signals by supporting insulin release from pancreatic β-cells and enhancing the sensitivity of target tissues/organs

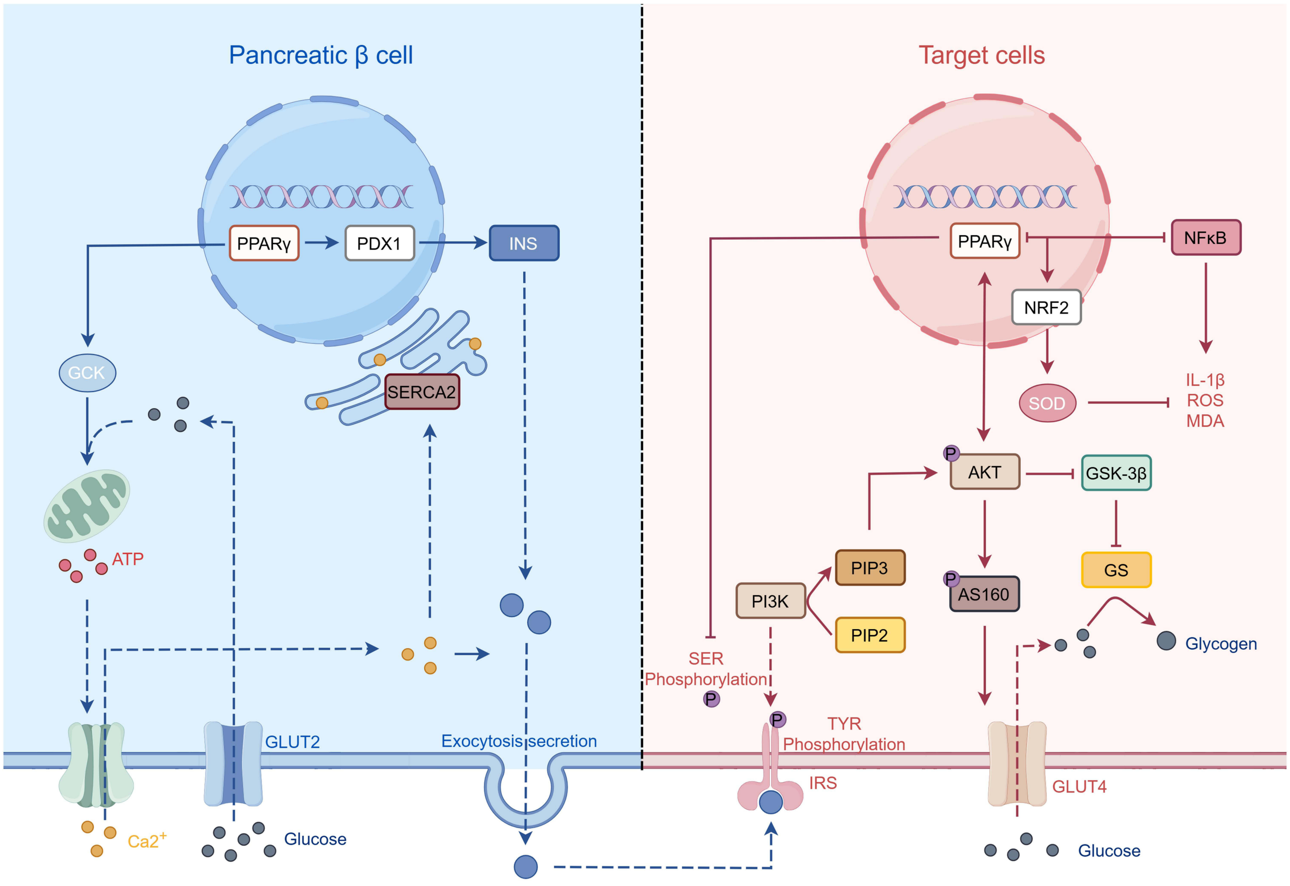

Figure 4 The role of PPARγ in islet cells and target organs.

to insulin. High insulin sensitivity ensures efficient glucose and lipid storage in hepatocytes and adipocytes, thereby maintaining low circulating levels of glucose and free fatty acids (FFAs). This helps mitigate the adverse effects of hyperglycemia and dyslipidemia. From the perspective of insulin signaling, PPARγ exerts a beneficial effect in preserving metabolic balance and preventing ectopic lipid deposition in non-adipose tissues.

Intestinal Tissue

Early studies on the relationship between the intestine and fatty liver were relatively limited. However, with the increasing recognition of the gut-liver axis, which connects the liver and intestine via the portal vein and bile ducts, the role of the intestine in maintaining normal liver function has become clearer. Recent research highlights the potential involvement of gut microbiota in the pathogenesis of fatty liver disease, suggesting that intestinal dysfunction and microbial imbalance may contribute to the development and progression of NAFLD.[104]

Maintaining the Intestinal Barrier

PPARγ is primarily expressed in colonic epithelial cells and plays a critical role in maintaining the intestinal barrier. It is a key regulator of mucosal defense, facilitating the release of mucus from goblet cells under pathological conditions.[105,106] The promoter sequence of α-defensin contains a PPRE,[107] and PPARγ knockout significantly reduces the levels of defensins.[105] Besides, PPARγ promotes the expression of Liver-Expressed Antimicrobial Peptide 2 (LEAP2) in intestinal cells, increasing its circulating levels.[108] PPARγ also inhibits NF-κB signaling-mediated oxidative stress and inflammation while promoting the expression of tight junction proteins (TJPs) such as claudin-3 and claudin-4, thus maintaining the integrity of the intestinal epithelial barrier.[109,110] Moreover, the expression of PPARγ in intestinal epithelial cells influences the composition and abundance of gut microbiota. The administration of rosiglitazone has been demonstrated to elicit a substantial reduction in the population of *Enterobacteriaceae* bacteria, encompassing both *Escherichia coli* and *Salmonella* species.[111,112] Increased abundance of *Enterobacteriaceae* is a core feature of the microbiome associated with histological changes in NAFLD[113] and correlates with the severity of the disease, particularly with *Escherichia coli*. Elevated *E. coli* levels are implicated in the activation of the Toll-like receptor 4/Nuclear factor kappa B (TLR4/NF-κB) signaling cascade and the concurrent suppression of the Wingless/beta-catenin (Wnt/β-catenin) pathway. These disruptions compromise the integrity of both the intestinal epithelial barrier and the gut-vascular barrier. This promotes bacterial translocation from the intestine to the liver via the portal vein, exacerbating hepatic steatosis, inflammation, and fibrosis.[114,115] PPARγ activation enhances the tricarboxylic acid (TCA) cycle in intestinal epithelial cells, reduces oxygen availability in the intestinal lumen, and decreases the release of iNOS and nitrates, inhibiting the growth and proliferation of *Enterobacteriaceae*.[106,116,117] Furthermore, PPARγ regulates the expression of various cytokines in intestinal epithelial cells, such as the stimulation of hepatocyte growth factor (HGF) release[118] and inhibiting the expression of follistatin, which contribute to the mitigation of gut dysbiosis and, consequently, the attenuation of hepatic steatosis progression.[119–122]

Reducing Intestinal Absorption of Exogenous Fats

NAFLD is closely associated with increased intake of exogenous lipids, with the intestine being the primary site of lipid absorption. PPARγ reduces cholesterol absorption by inhibiting the SP-1/SREBP-2/NPC1L1 signaling pathway in intestinal epithelial cells.[123] It also suppresses SREBP-2 and its downstream targets, including HMG-CoA reductase and LDL receptors, reducing cholesterol synthesis in cells.[124] Besides, PPARγ decreases paracellular permeability in intestinal epithelial cells, limiting lipid entry into the bloodstream via the paracellular route.[125] Accumulation of cholesterol, particularly free cholesterol, in intestinal tissue correlates with the occurrence and severity of NAFLD. Free cholesterol that enters hepatocytes impairs mitochondrial membrane potential, increases ROS levels, and disrupts lysosomal lipophagy, leading to lipid accumulation in hepatocytes and eventually causing hepatocyte apoptosis.[126] Although PPARγ is generally associated with increased fatty acid uptake, a conditional knockout study in intestinal epithelial cells showed that PPARγ deletion accelerated intestinal transit, resulting in elevated plasma triglyceride and free fatty acid levels.[127] This suggests that PPARγ plays a crucial role in stabilizing systemic lipid metabolism by controlling intestinal absorption of FFAs.

In summary, intestinal PPARγ demonstrates a protective effect against the initiation and advancement of NAFLD by strengthening the intestinal mucus barrier, limiting the proliferation and movement of anaerobic bacteria, modulating cytokine production in intestinal epithelial cells, and regulating lipid absorption, thereby mitigating NAFLD and NASH (Figure 5).

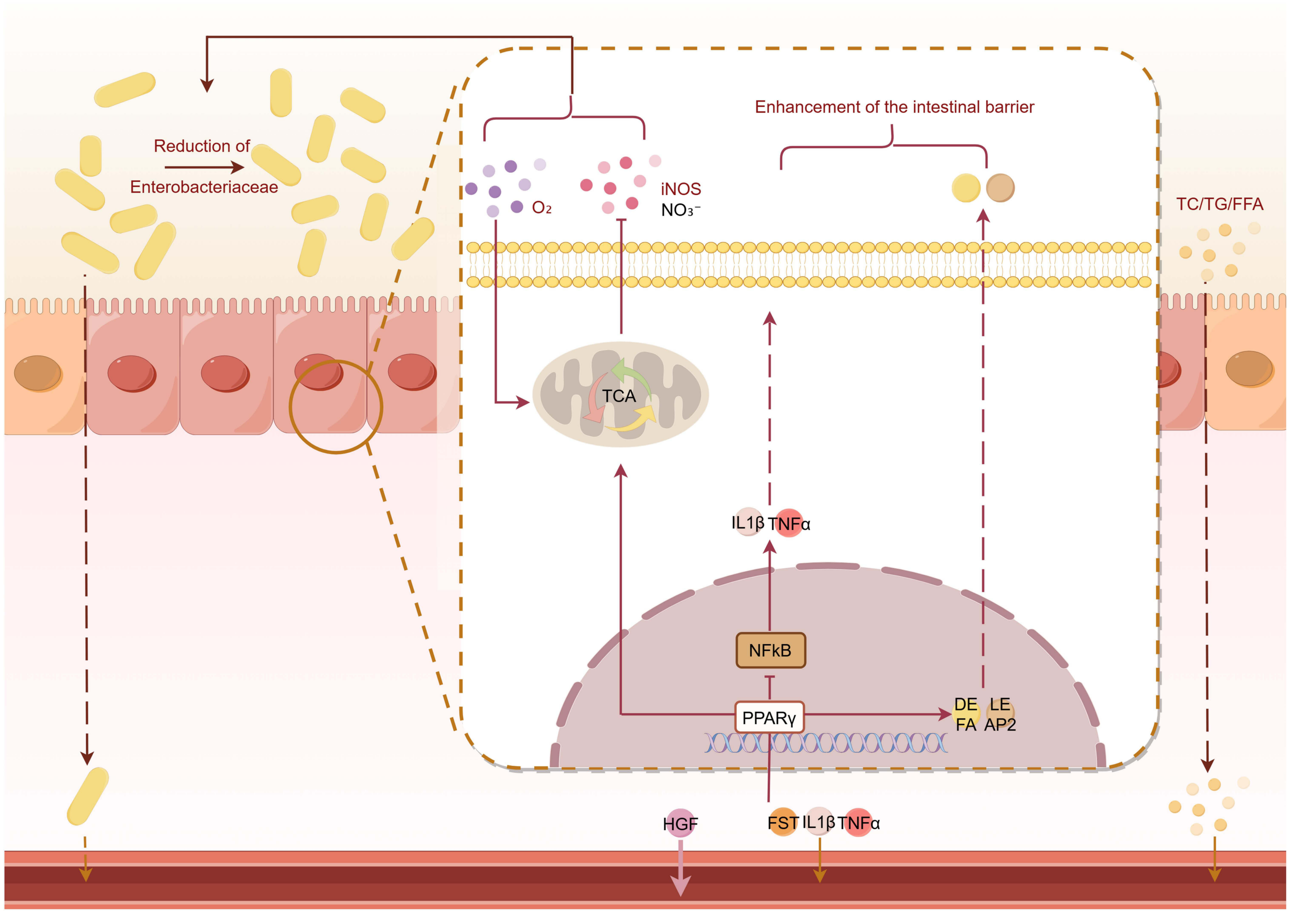

Figure 5 The role of PPARγ in the intestine.

Immune Cells

Mitigating Excessive Immune Activation Mediated by Immune Cells

In addition to parenchymal cells, various immune cells are distributed throughout tissues, and dysregulated activation of these immune cells, coupled with persistent inflammation and compromised tissue function, are recognized as substantial contributors to the pathogenesis of NAFLD. For instance, cytokines derived from immune cells, such as TNF-α and IL-1β, are key mediators of insulin resistance within hepatocytes. They disrupt insulin signaling pathways via the activation of NF-κB. Initial investigations underscored the importance of PPARγ in lipid metabolism and insulin signaling. However, more recent research has shifted its focus to its immunomodulatory roles, particularly within immune cell populations. PPARγ participates in the effector mechanisms of granulocytes, lymphocytes, macrophages, and dendritic cells (DCs), exhibiting a dualistic regulatory capacity. Firstly, PPARγ demonstrates high expression levels in various immune cells and is crucial for the generation of appropriate immune responses. PPARγ deficiency results in aberrant differentiation and development of helper T cells, leading to a significant depletion in their numbers. PPARγ is also essential for the antigen-presenting function of DCs, and its deletion abolishes this function.[128] On the other hand, PPARγ activation exerts immunosuppressive and anti-inflammatory effects on multiple immune cells. Activation of PPARγ reduces the abundance or function of T/B cells and granulocytes, weakens the T cell-stimulating ability of DCs, and promotes the alternative activation of macrophages toward the M2 phenotype.[129,130] Among these effects, the effect of PPARγ on macrophage polarization within the context of hepatic steatosis, inflammation, and fibrosis has become a subject of considerable interest. In individuals with NAFLD, a preponderance of M1 macrophages and a relative scarcity of M2 macrophages are typically observed. Elevated PPARγ activity facilitates a shift in hepatic macrophage populations from the M1 to the M2 phenotype, resulting in a reduction of hepatic steatosis and improved insulin sensitivity.[131] This effect is primarily due to PPARγ's function as a transcription factor that suppresses pro-inflammatory cytokines and promotes the expression of immune tolerance factors.[132] However, the role of macrophage phenotypes (M1/M2) in fibrosis remains controversial. While macrophages are considered a major source of TGF-β1 and PDGF, both of which contribute to fibrosis,[133] the effects of M1 and M2 phenotypes on liver fibrosis are complex and context-dependent. Studies have shown that both M1 and M2 phenotypes can modulate liver fibrosis progression,[134] likely due to the highly heterogeneous subpopulations of macrophages in fatty liver disease.[24]

Current research highlights that PPARγ plays a critical role in immune cell activation. Its activation, particularly in the context of NAFLD, is widely recognized for its anti-inflammatory effects. PPARγ activation has potential therapeutic significance in mitigating inflammation and oxidative stress induced by lipid accumulation, thus preventing the progression from simple steatosis to steatohepatitis and even cirrhosis.

Summary

In summary, PPARγ plays a pivotal role in preventing the progression of NAFLD to NASH by exerting clear anti-inflammatory and anti-fibrotic effects. PPARγ agonists can mediate these effects through multiple mechanisms, including suppression of pro-inflammatory cytokine expression, modulation of macrophage polarization from the M1 to the M2 phenotype, regulation of adipokine release from adipose tissue, and attenuation of hepatic inflammation. Additionally, PPARγ agonists inhibit hepatic stellate cell activation and collagen deposition, thereby alleviating liver fibrosis. These mechanisms underscore the protective role of PPARγ in the NASH stage.

Notably, during the progression from NAFLD to NASH, circulating levels of free fatty acids (eg, palmitic acid) and certain adipokines (eg, leptin) increase significantly. These factors not only promote hepatic inflammation and cellular injury but also suppress the expression and activity of PPARγ, further aggravating disease progression. This down-regulation of PPARγ signaling has been observed in both clinical samples and in vivo and in vitro models, suggesting that the NASH stage is characterized by impaired PPARγ activity. Therefore, restoring PPARγ function via pharmacological activation provides a sound physiological and pathological rationale for the use of PPARγ agonists in NASH therapy.

On the other hand, although some studies suggest that PPARγ may exacerbate hepatic lipid accumulation by promoting lipid uptake and synthesis in the liver, this "lipid-promoting" effect is better understood as part of a compensatory systemic metabolic regulatory mechanism. PPARγ plays a critical role as a transcription factor in insulin signaling pathways, transducing signals via the NEDD4/AKT cascade to enhance hepatic glucose uptake.[135] However, under conditions of insulin resistance, the liver's glycogen storage capacity becomes impaired, leading to persistent hyperglycemia. This chronic elevation in blood glucose triggers continuous insulin secretion by pancreatic β-cells, resulting in hyperinsulinemia. As the primary organ exposed to high portal insulin concentrations, the liver exhibits pathological upregulation of PPARγ, contributing to hepatic steatosis. Thus, PPARγ-mediated lipid accumulation in the liver can be viewed as a physiological adaptation to a hyperglycemic environment. Modulating circulating levels of free fatty acids (FFAs) may help alleviate hepatic steatosis caused by PPARγ overactivation.

Importantly, as a central regulator of systemic metabolism, PPARγ also reduces dietary lipid absorption in the intestine, enhances lipid storage, and inhibits lipolysis in adipose tissue, thereby lowering circulating FFA levels. This systemic effect reduces the liver's passive uptake of FFAs, interrupting the initial pathogenic trigger of FFA induced hepatic lipid deposition. Therefore, from a systemic metabolic perspective, PPARγ agonists not only offer therapeutic benefit in the NASH stage but also hold potential for preventing and managing early-stage NAFLD by targeting upstream metabolic disturbances (Figure 6).

To further explore the role of PPARγ activation in NAFLD, we have reviewed and summarized clinical studies on PPARγ agonists.

Clinical Application of PPARγ Agonists

As summarized in the Table 1 above, multiple PPARγ agonists are currently undergoing clinical trials for NAFLD treatment. These include PPARγ mono-agonists (Pioglitazone and Rosiglitazone), PPARα/γ dual agonists (Aleglitazar and Fenofibrate), and PPAR pan-agonists (Lanifibranor). However, the development of several dual/pan-agonists, such as Seladelpar (a PPARδ-selective agonist) and Elafibranor (a PPARα/δ dual agonist), has been terminated due to severe side

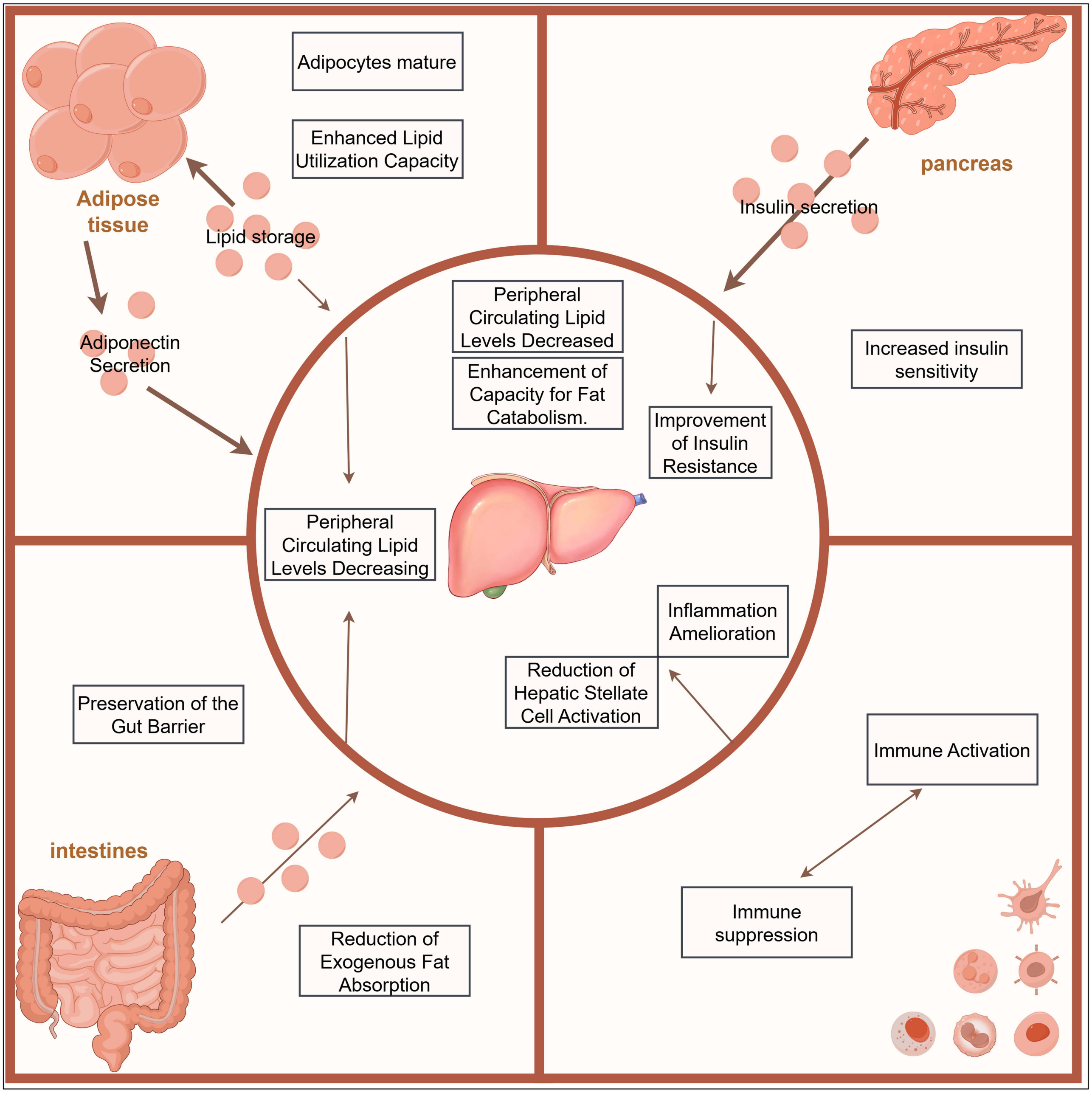

Figure 6 The role of PPARγ in NAFLD.

effects or lack of efficacy.[136] Clinical trials and meta-analyses indicate that agonists with PPARγ activity significantly lower blood lipids and glucose levels, improve liver function, and reduce inflammation. While their effects on hepatic fat accumulation and fibrosis vary, most studies support their beneficial role in both aspects.

Pioglitazone is recommended in several clinical guidelines for the management of NAFLD/NASH treatment.[9,10] A 2017 expert consensus further suggested the applicability of PPARγ agonists, including pioglitazone, in both individuals with and without type 2 diabetes mellitus.[157] In NAFLD patients exhibiting insulin resistance, PPARγ agonists have been shown to induce the most substantial reduction in hepatic steatosis compared with other antidiabetic agents, such as sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, biguanides, sulfonylureas, and insulin.[158]

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Table 1 Clinical Study of PPARγ Agonists

Drug Name	Category	Activation Effect[136]	Conclusion	Article Type
Pioglitazone	PPARγ Mono-Agonist	α25.2%, δ0.518%, γ104% PCG-1α>70%, SRC1>20%	Oral Glucose Tolerance Test (OGTT) showed a reduction in blood glucose levels; ALT levels decreased; Improvements in steatosis, ballooning degeneration, and lobular inflammation were observed[137]	RCT
			The levels of fasting blood glucose, ALT, AST, γ-glutamyltransferase, and triglycerides were reduced, and insulin resistance was improved[138]	META
			PPARγ activation-mediated improvements in tissue pathology, liver enzymes, HOMA-IR, and reductions in blood lipids were consistent in both non-diabetic NAFLD patients and diabetic NAFLD patients. The incidence of edema was higher in the pioglitazone group[139]	META
			Improvement in left ventricular mechanics in undiagnosed ASCVD patients[140]	PCS
			Fatty degeneration, inflammation, ballooning, and improvement in liver function; reduction in blood glucose; no significant improvement in fibrosis markers[141]	META
			One year of low-dose pioglitazone treatment significantly improved hepatic fat degeneration and inflammation, as well as systemic and adipose tissue insulin resistance. The beneficial effects of pioglitazone on NAFLD were independent of blood glucose control[142]	RCT
			Compared to the tofogliflozin group, pioglitazone treatment showed no significant difference in improving hepatic fat degeneration and blood glucose levels, but it significantly increased adiponectin and HDL levels, and notably reduced triglyceride levels, although it caused weight gain[143]	PCS
			Pioglitazone shows better efficacy in women[144]	RCT
			Pioglitazone is the optimal therapy for treating steatosis and alleviating lobular inflammation[145]	META
			Decreased Bone Mineral Density (BMD) in the lumbar spine[146]	PCS
			Serum ALT levels, HbA1c, and fasting blood glucose were reduced; there was no significant reduction in visceral fat area[147]	PCS
			The prevalence of bladder cancer was very low in diabetic patients exposed to (or not exposed to) pioglitazone (<0.3%), and the beneficial effects of the drug on CVD and NASH were much greater. Therefore, the use of pioglitazone should be resumed[148]	META
Rosiglitazone	PPARγ Mono-Agonist		Overall improvement in fatty degeneration, hepatocyte inflammation, ballooning degeneration, and fibrosis; serum transaminases were reduced[149]	PCS
Saroglitazar	PPARα/γ Dual-Agonist	α/δ13.3%, γ为24.9%PCG-1α <50%, SRC1<50%	Improvement in liver enzymes, serum glucose, and lipid profile, along with reduced liver stiffness, with no significant adverse effects[150]	META
			ALT, liver fat content, insulin resistance, and atherogenic dyslipidemia were improved[151]	RCT
			Regardless of weight loss, significant reductions were observed in CAP value, ALT, AST, HbA1c, LDL, total cholesterol, and triglyceride levels[152]	PCS

(*Continued*)

Table 1 (Continued).

Drug Name	Category	Activation Effect[136]	Conclusion	Article Type
lanifibranor	PPAR Pan-Agonist	α56.4%, γ89.4%, δ6.0% PCG-1α >100%, SRC1<50%	Liver enzyme levels were reduced, with improvements in lipids, inflammation, and fibrosis[153]	RCT
Aleglitazar	PPARα/γ Dual-Agonist		Improvements in hepatic steatosis and fibrosis[154]	RCT
Fenofibrate	PPARα(/γ Dual) Agonist		Serum triglyceride levels were reduced, but the overall liver volume and total liver fat volume increased.[155]	RCT
			Inflammatory factors (TNF-α), liver function (ALT, AST, GGT), markers related to matrix deposition (HA), liver fibrosis-associated cytokine (TGF-β1), lipid profile (total cholesterol, TG, LDL-C), blood glucose levels (FPI, FBG, HOMA-IR), and liver stiffness were significantly reduced; HDL-C was significantly increased.[156]	PCS

Abbreviations: RCT, randomized controlled trial; META, Meta-analysis; PCS, Prospective Clinical Study.

Among dual agonists, Saroglitazar (a PPARα/γ agonist) exhibits glucose-lowering effects comparable to Rosiglitazone while offering superior lipid-lowering benefits without the weight gain commonly associated with full PPARγ agonists.[159] Recently, Saroglitazar was approved in India as a treatment option for fatty liver disease.[160] A network meta-analysis further demonstrated that Saroglitazar outperforms GLP-1 agonists and metformin in protecting hepatocytes and reducing circulating triglycerides, ALT, and AST levels.[161]

In summary, both full and partial PPARγ agonists exhibit strong therapeutic potential in NAFLD by modulating metabolic processes, improving insulin sensitivity, and mitigating hepatic inflammation and fibrosis.

Safety Profile of PPARγ Agonists

While PPARγ agonists have shown promising therapeutic effects in NAFLD clinical trials, their clinical use is limited by systemic side effects associated with PPARγ activation, including cardiovascular risks, fracture risks, and tumorigenic effects.

Cardiovascular Risks

Concerns regarding the cardiotoxicity of PPARγ agonists mainly arise from the higher incidence of edema and congestive heart failure (CHF) observed with TZD treatment. In 2007, two randomized controlled trials revealed that rosiglitazone use in diabetic patients was linked to a higher incidence of edema, increased risk of heart failure, and greater use of anti-heart failure medications. This prompted the FDA to restrict the use of rosiglitazone in 2010.[162,163] However, after a re-evaluation of previous studies, the FDA concluded there was insufficient evidence to indicate an increased risk of myocardial infarction with rosiglitazone compared to metformin and sulfonylureas, resulting in the subsequent removal of these restrictions.[164] Nonetheless, the debate regarding the cardiovascular risks associated with rosiglitazone and other TZDs persists.

Two recent meta-analyses on rosiglitazone and cardiovascular risks confirmed its association with CHF and myocardial infarction.[165,166] The potential for rosiglitazone to induce heart failure is primarily attributed to its fluid retention properties. Studies have demonstrated that reductions in plasma volume can attenuate TZD-induced volume expansion and associated adverse cardiac events.[167] Research indicates that rosiglitazone induces fluid retention through renal and vascular mechanisms. Specifically, it stimulates sodium reabsorption via the epithelial sodium channel (ENaC) and NKCC2, and water reabsorption via aquaporins, through the PPARγ/src/EGFR/ERK pathway.[168–170] Moreover, it promotes AKT phosphorylation and epidermal growth factor secretion, increasing vascular endothelial cell migration and permeability, which predisposes patients to fluid retention and CHF.[171] Furthermore, rosiglitazone activates mTOR, increasing cardiac myofibrillar protein content, and promotes MAPKp38 and H3 histone phosphorylation, contributing to cardiac hypertrophy.[172] It also inhibits vascular K(ATP) channels, impairing coronary artery responsiveness to vasodilatory signals and raising the risk of cardiovascular ischemia.[173] Moreover, rosiglitazone strongly activates TRPC5, a protein found to be upregulated in cardiomyocytes of patients with heart failure and obstructive sleep apnea. TRPC5 exacerbates oxidative stress and calcium overload, further contributing to myocardial injury and hypertrophy.[174–176] In contrast, other PPARγ agonists like pioglitazone, troglitazone, and certain natural agonists do not activate TRPC5.[177]

The effects of TZDs, such as rosiglitazone, are mediated through both PPARγ-dependent and PPARγ-independent mechanisms.[178] While fluid retention is primarily a PPARγ-dependent effect,[170,179] TZDs also exhibit PPARγ-independent direct ERK activation,[180] which may account for the observed variations in edema-inducing potential among different PPARγ agonists. Notably, PPARγ itself is not directly implicated in the activation of mTOR and MAPK pathways. Some studies suggest that PPARγ inhibits p38 phosphorylation via the CXCL13-CXCR5 pathway,[181] and its expression is inversely correlated with mTOR expression.[182] Early research found that various PPARγ ligands reduced tissue necrosis associated with acute myocardial infarction,[183] highlighting the potential benefits of PPARγ activation in preventing coronary heart disease and cardioprotection. PPARγ overexpression promotes PRKAG2 expression in cardiomyocytes, leading to enhanced AMPK activity and a reduction in hypoxia-induced damage.[184] It also inhibits JNK and AP-1 activity, reducing inflammation and apoptosis, thereby limiting ischemic heart injury.[185] These findings suggest that the heart failure and myocardial damage observed with rosiglitazone and other TZDs may be, at least in part, independent of PPARγ activation. Minimizing the off-target effects of these drugs could potentially mitigate some of their associated adverse events.

Current evidence suggests that PPARγ-induced renal tubular sodium reabsorption is insulin-dependent,[186] which may account for the observed significant increase (approximately 15%) in the incidence of peripheral edema when TZDs are administered in conjunction with insulin therapy.[187] This parallels insulin's role in the liver, where elevated insulin levels promote hepatic fat deposition. Similarly, type 2 diabetic patients—who often exhibit hyperinsulinemia—have a higher prevalence of NAFLD compared to type 1 diabetic patients (40.4% vs 19.3%),[188] underscoring the importance of controlling insulin levels when using TZDs.

Conversely, some studies support the positive effects of PPARγ agonists on cardiovascular health. A prospective study by Kemal et al found that plasma BNP levels increased and myocardial performance index decreased during the first three months of rosiglitazone treatment but stabilized and improved after six months.[189] Other studies have shown that TZDs reduce carotid intima-media thickness (CIMT),[190] prevent atrial fibrillation,[191] and lower cardiometabolic risk by promoting visceral-to-subcutaneous fat redistribution.[192] Rosiglitazone also reduces both resting and exercise blood pressure in type 2 diabetic patients.[193] Importantly, the adverse effects of rosiglitazone-induced fluid retention do not appear to significantly impair cardiac pump function, as demonstrated by the relative stability of left ventricular ejection fraction (LVEF). Rosiglitazone's ability to sensitize the atrial natriuretic peptide (ANP) response suggests a potential for protective cardiovascular effects. Moreover, the edema and heart failure manifestations associated with rosiglitazone therapy are often reversible with diuretic intervention, indicating that the use of TZDs in the management of CHF may carry less risk than previously considered.[163,194]

Fracture Risk

Fractures represent a significant risk associated with TZDs,[195,196] and this effect primarily affects women, with a disproportionate impact on women. This fracture risk is primarily attributed to the potent activation of PPARγ. As part of the normal aging process, bone marrow stromal cells (BMSCs) tend to differentiate more into adipocytes rather than osteoblasts, leading to reduced bone formation and an increased risk of osteoporosis and fractures.[197] Mesenchymal stem cells (MSCs), the common progenitor cells for both adipocytes and osteoblasts, exhibit an inverse relationship between adipogenic and osteogenic differentiation. PPARγ and Wnt signaling pathways govern MSC differentiation, with PPARγ activation favoring adipocyte differentiation,[198] thus reducing the pool of osteogenic cells. Furthermore, PPARγ has been implicated in osteoclast activation. It directly regulates the c-fos/NFATc1 signaling pathway, a crucial transcriptional signal for osteoclast differentiation, leading to increased osteoclast activity. Conversely, PPARγ inhibition significantly attenuates osteoclast activation.[199,200] Traditional TZDs, as full PPARγ agonists, reduce bone mass by decreasing osteoblast activity and increasing osteoclast activation, thereby promoting osteoporosis and increasing the risk of fractures.

In contrast, novel partial PPARγ agonists, such as MSDC-0602K, CMHX008, and SR10171, exhibit weak binding affinity to PPARγ, thereby avoiding adipogenic induction in BMSCs while concurrently improving insulin resistance and glucose/lipid metabolism.[201–203] The differential effects of these novel partial agonists compared to traditional full agonists on bone mass are primarily attributable to their influence on the phosphorylation status of the PPARγ S112 site. Dephosphorylation and activation of the S112 site enhance PPARγ's adipogenic transcriptional activity, consequently reducing osteoblast differentiation. Conversely, when this site remains phosphorylated and inactive, PPARγ's adipogenic activity is suppressed, and BMSC differentiation is unaffected,[203] suggesting that partial PPARγ activation can circumvent the bone loss typically associated with full activation. Furthermore, physical exercise has been shown to significantly suppress bone marrow adipose tissue volume and promote bone formation. The combination of exercise therapy with PPARγ agonist treatment may therefore offer a strategy to mitigate the skeletal effects of these drugs.[204,205]

Tumor Risk

The potential for increased tumor risk associated with PPARγ activation, particularly with pioglitazone, has generated concern, notably regarding its possible association with bladder cancer—a risk not observed with other TZDs such as rosiglitazone.[206,207] The relationship between pioglitazone and bladder cancer remains controversial. While several meta-analyses have reported a significant correlation,[208] others have found no such association.[209] Conversely, a 2024 meta-analysis from Taiwan suggested that pioglitazone use is associated with a decreased incidence of various cancers, including breast and prostate cancer.[210] Some investigators have posited that, due to the substantial heterogeneity observed across clinical studies, these data should not be aggregated, and that further rigorous observational studies are required.[211] Furthermore, a 2018 meta-analysis concluded that while pioglitazone use for longer than one year is associated with an increased risk of bladder cancer, the overall incidence remains low (less than 0.3%). The authors emphasized that considering pioglitazone's established benefits in the management of cardiovascular disease and NAFLD, its clinical utility in the treatment of metabolic disorders is supported.[148]

However, the preponderance of in vitro and in vivo studies supports the anti-tumorigenic effects of PPARγ agonists, including pioglitazone, even in the context of bladder cancer. Shidong Lv et al found that PPARγ functions as a favorable prognostic indicator in bladder cancer patients, and its activation inhibits bladder cancer cell proliferation and promotes apoptosis via the PI3K-Akt pathway.[212] A comprehensive proteomic analysis of normal human bladder epithelial cells revealed no evidence of pioglitazone-induced bladder tumorigenesis.[213] Pioglitazone has been shown to reduce biomarkers associated with cancer-associated fibroblasts and tumor hepatocytes, thereby inhibiting tumor growth.[214,215]

Summary

In summary, concerns regarding the cardiovascular, skeletal, and oncological risks associated with PPARγ agonists are substantiated. However, these concerns should not preclude the continued development and clinical application of these agents for the treatment of hepatic steatosis. Certain adverse effects observed with currently available drugs arise from mechanisms independent of PPARγ activation or result from full PPARγ agonism, both of which may be mitigated through refined drug design. Furthermore, the concurrent administration of diuretics, calcium supplementation, and exercise regimens can effectively minimize adverse events. Therefore, while ongoing surveillance for adverse effects associated with PPARγ agonists remains essential, these risks should no longer constitute an impediment to their development or clinical use in the treatment of metabolic diseases, including NAFLD.

Research and Development Direction

The activation effects of PPARγ are intrinsically linked to its baseline expression levels within specific tissues. In cell lines exhibiting low endogenous PPARγ expression, such as Caco-2 and DLD-1, PPARγ overexpression has been shown to inhibit cellular proliferation. Conversely, this inhibitory effect is not observed in cell lines with inherently high PPARγ expression, such as HT-29 and LOVO cells.[216] Even within a single organ, PPARγ expression and its consequent effects can demonstrate significant regional variation. For instance, within the colon, PPARγ expression is considerably higher in proximal colon tissue compared to distal colon tissue. In the proximal colon, PPARγ primarily governs metabolic

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functions, whereas, in the distal colon, its principal role shifts towards the modulation of signal transduction, cellular adhesion, and motility.[217] This highlights the importance of tissue specificity in PPARγ's functional roles.

Furthermore, differences in PPARγ expression levels in liver tissues among individuals can influence the therapeutic effects of PPARγ agonists, such as TZDs. Gao et al demonstrated that rosiglitazone exerted anti-steatotic effects in mice with low hepatic PPARγ expression but promoted hepatic steatosis in mice with high hepatic PPARγ expression. They suggested that patients with low hepatic PPARγ levels may benefit more from PPARγ agonist therapy.[218] Furthermore, knockout of PPARγ in hepatocytes reduced the lipogenic effects of short-term TZD treatment and enhanced the therapeutic effects of rosiglitazone and other TZDs on extrahepatic tissues and non-parenchymal cells.[219,220] This underscores the pivotal role of hepatocyte PPARγ expression levels in determining the therapeutic efficacy of PPARγ agonists. Therefore, individual hepatic PPARγ levels should be taken into account when prescribing PPARγ agonists for NAFLD treatment, although further research is required to determine the optimal PPARγ expression levels for agonist therapy.

Moreover, the varying effects of PPARγ activation on NAFLD in pharmacological studies may be attributed to differences in experimental models and target tissues. Chihiro Ebihara et al proposed that, in mouse models, TZD treatment increases hepatic PPARγ levels, while in rat models and NAFLD patients, PPARγ upregulation primarily occurs in adipose tissue with little change in hepatic PPARγ levels.[221] This suggests that rat models may be more suitable for studying the effects of PPARγ-targeting drugs like TZDs in NAFLD. Furthermore, this evidence supports the concept of tissue-specific PPARγ sensitivity, indicating that targeting PPARγ in specific tissues could provide a promising direction for future drug development.[222,223]

PPARγ agonists exert their effects by binding to the PPARγ ligand-binding domain (LBD), inducing conformational changes that facilitate transcriptional activation. Compared to traditional full agonists, novel partial PPARγ agonists differ primarily in their binding sites. Full agonists bind to the classical ligand-binding pocket near the AF-2 helix (H12 helix) of the LBD, stabilizing the H12 conformation and fully activating PPARγ transcriptional activity. In contrast, partial agonists bind to a pocket near the Ω loop between helices H2' and H3, which does not stabilize the H12 conformation, resulting in partial (selective) activation of PPARγ transcriptional activity[224](Figure 7B–D). As a result, partial agonists recruit fewer coactivators and induce less PPARγ dephosphorylation.

Nuclear transcription factors, including PPARγ, rely on coactivators to exert their transcriptional effects. The recruitment of different coactivators is a key factor in the biased signaling of nuclear transcription factors.[225] Differences in coactivator recruitment can help explain the varying effects of PPARγ agonists. For example, the full agonist rosiglitazone and the partial agonist MRL24 exhibit biased recruitment of 100 to 300 coactivator residue regions, leading to less activation of metabolic pathways by MRL24 and the absence of obesity induction.[226] Post-translational modifications (PTMs) also play a role in the selective activation of PPARγ, enabling insulin sensitization while avoiding the side effects of TZDs.[227] Among these, the phosphorylation status of PPARγ at specific sites has been extensively studied (Figure 7A). For instance, phosphorylation at S84 is linked to cell proliferation, while dephosphorylation at T166 is associated with lipid metabolism, promoting macrophage repair and tissue regeneration,[228] and inducing beige adipogenesis to ameliorate obesity-related metabolic disorders.[229] S112 dephosphorylation effectively inhibits tumor cell proliferation,[230] and as mentioned earlier, S112 is involved in adipogenic induction in mesenchymal stem cells. Maintaining its phosphorylation state reduces adipocyte formation and promotes osteogenic differentiation of bone marrow stromal cells. S273 is a key site that regulates insulin sensitivity, with dephosphorylation conferring constitutive activity to PPARγ, upregulating insulin sensitivity-related gene expression, and maintaining high insulin sensitivity in cells and tissues.[231] The phosphorylation status of these sites determines the biological functions of PPARγ. Specifically, in the treatment of NAFLD, low transactivation may reduce hepatic steatosis.[232] Therefore, effective PPARγ agonists for NAFLD treatment should possess a specific pharmacological profile. These agents should demonstrate minimal transactivation potential, ideally by avoiding direct interaction with the H12 domain while simultaneously and effectively inhibiting S273 phosphorylation. From a structural perspective, these therapeutic molecules should incorporate hydrophobic moieties to mitigate transactivation by preventing binding to arm I of the PPARγ receptor. Concurrently, they should feature structural elements that facilitate interactions with arm II and establish hydrogen bonds with corresponding residues in arm III, thereby achieving a degree of partial PPARγ activation.[233]

Combination therapies represent a promising approach for the future application of PPARγ agonists. For example, the combination of tofogliflozin and pioglitazone has demonstrated superior efficacy in reducing triglyceride levels,

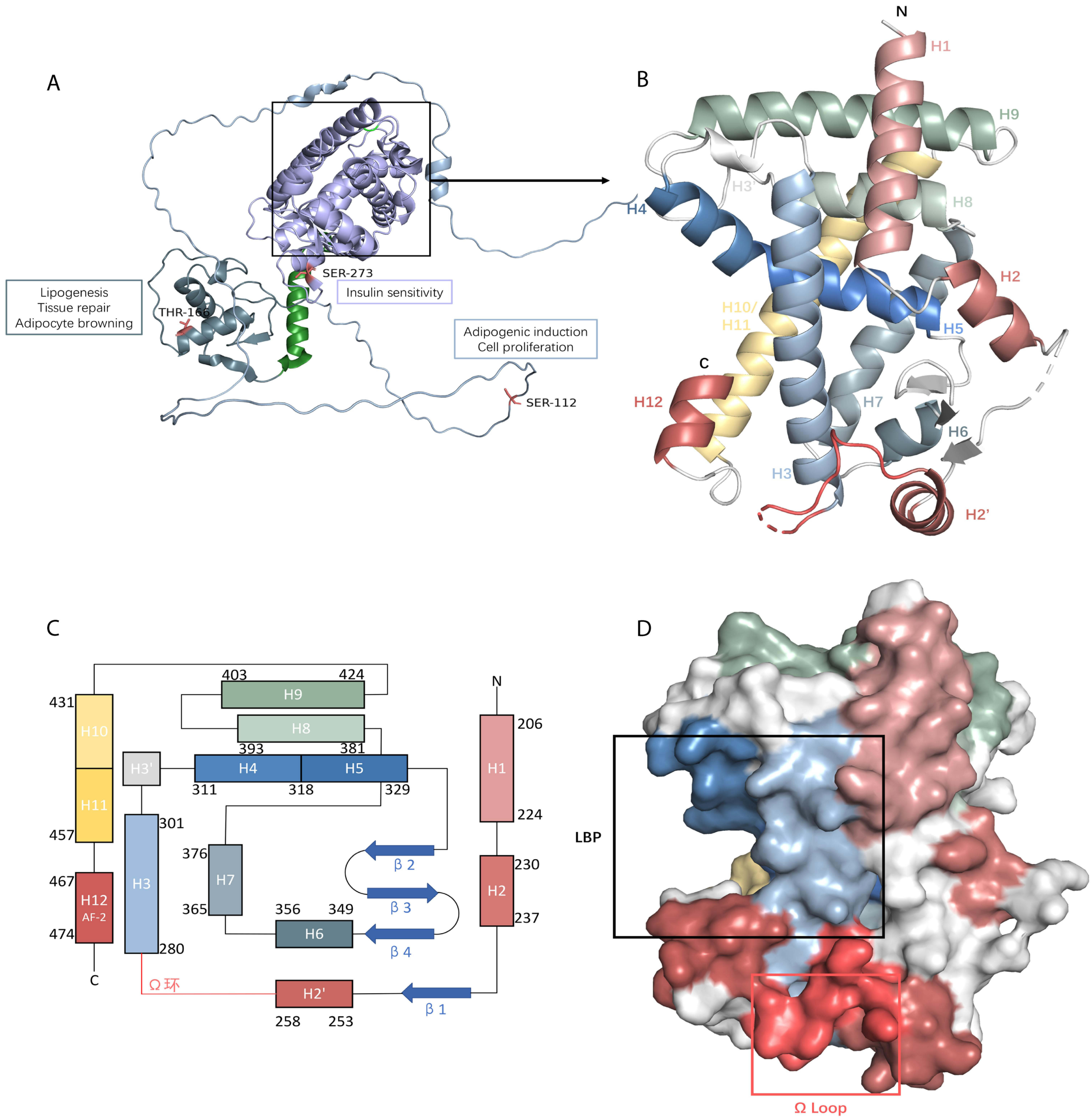

Figure 7 PPARγ and its Ligand-Binding Domain (LBD) structure. (**A**) The full-length predicted structure of human PPARγ obtained from the AlphaFold Protein Structure Database.[195] (**B**) The crystal structure of the PPARγ Ligand-Binding Domain (LBD) obtained from the Protein Data Bank (PDB ID: 6L8B).[196] (**C**) A schematic planar representation of the PPARγ structure showing its functional domains. (**D**) Three-dimensional view of the LBD pocket (LBP) and the Ω-loop region.

increasing high-density lipoprotein (HDL) cholesterol and adiponectin concentrations, and elevating ketone body production, while simultaneously counteracting pioglitazone-associated weight gain and conferring cardioprotective benefits.[234] Alternatively, combining PPARγ agonists with diuretics, calcium supplements, vitamin D, or exercise therapy can alleviate the adverse effects associated with full agonist activity.

Conclusion

Given the multifaceted role of PPARγ, PPARγ agonists hold significant therapeutic potential for NAFLD. We suggest focusing future research and drug development efforts on: (1) achieving tissue-selective PPARγ activation, particularly targeting adipose tissue for its critical role in fat redistribution, while carefully avoiding full hepatic PPARγ activation due to its complex, sometimes contradictory, effects; (2) thoroughly investigating how ligand binding to both traditional and non-canonical regions of the PPARγ ligand-binding domain influences PPARγ's shape and biological activity, with the goal of minimizing unwanted transactivation in new drugs; (3) delving into the interplay between PPARγ activation, coactivators, and site-specific dephosphorylation, recognizing that the balance of coactivators and phosphorylation can significantly shift PPARγ's impact on downstream targets, especially concerning fat transport, synthesis, breakdown, and β-oxidation; (4) increasing the use of rat models, which often provide more human-relevant responses, in PPARγ agonist studies; (5) identifying the factors that control hepatic PPARγ expression, as individuals with naturally lower hepatic PPARγ levels might be better candidates for PPARγ agonist therapy for metabolic diseases, given the potential downsides of hepatic PPARγ activation; and (6) developing strategies, such as combination therapies, to minimize the side effects associated with systemic PPARγ activation.

Disclosure

All authors report no conflicts of interest in this work.

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