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## The roles of PPAR $\gamma$ and its agonists in autoimmune diseases: A comprehensive review



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### ABSTRACT

Autoimmune diseases are common diseases of the immune system that are characterized by the loss of self-tolerance and the production of autoantibodies; the breakdown of immune tolerance and the prolonged inflammatory reaction are undisputedly core steps in the initiation and maintenance of autoimmunity. Peroxisome proliferator-activated receptors (PPARs) are ligand-dependent transcription factors that belong to the nuclear hormone receptor family and act as ligand-activated transcription factors. There are three different isoforms of PPARs: PPAR $\alpha$ , PPAR $\gamma$ , and PPAR $\beta/\delta$ . PPAR $\gamma$  is an established regulator of glucose homeostasis and lipid metabolism. Recent studies have demonstrated that PPAR $\gamma$  exhibits anti-inflammatory and anti-fibrotic effects in multiple disease models. PPAR $\gamma$  can also modulate the activation and polarization of macrophages, regulate the function of dendritic cells and mediate T cell survival, activation, and differentiation. In this review, we summarize the signaling pathways and biological functions of PPAR $\gamma$  and focus on how PPAR $\gamma$  and its agonists play protective roles in autoimmune diseases, including autoimmune thyroid diseases, multiple sclerosis, rheumatoid arthritis, systemic sclerosis, systemic lupus erythematosus, primary Sjogren syndrome and primary biliary cirrhosis.

### 1. Introduction

Autoimmune diseases are a wide spectrum of diseases that are characterized by the loss of self-tolerance and the production of autoantibodies [1]. There are both organ-specific autoimmune diseases, such as autoimmune thyroid diseases, multiple sclerosis and rheumatoid arthritis, and systemic autoimmune diseases, such as systemic sclerosis and systemic lupus erythematosus [2]. Although the pathogenic mechanisms underlying autoimmune diseases remain to be elucidated, the breakdown of immune tolerance and the prolonged inflammatory reaction are undisputedly core steps in the initiation and maintenance of autoimmunity [3]. Thus, the molecules that participate in immune feedback may be potential therapeutic targets for the treatment of autoimmune diseases.

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors which belong to the nuclear hormone receptor family [4]. There are three different isoforms of PPARs, namely, PPAR $\alpha$ , PPAR $\beta/\delta$  and PPAR $\gamma$ , all of which are encoded by different genes [5]. These isoforms heterodimerize with the retinoid X receptor. When activated, this complex can regulate gene expression by binding to specific peroxisome proliferator response elements (PPREs), which

are located in the regulatory site of each gene [6]. Although the three different isoforms of PPARs share a high degree of structural similarity, they have different ligands and distinct patterns of distribution [7]. PPAR $\alpha$  was the first PPAR subtype to be cloned. The basic function of PPAR $\alpha$  is to regulate the oxidation of fatty acids. PPAR $\alpha$  is highly expressed in multiple organs and tissues, particularly in the liver, heart, kidneys, brown adipose tissue and skeletal muscles [8]. PPAR $\beta/\delta$  not only takes part in the metabolism of lipids but is also involved in many other physiological processes, such as wound healing, embryonic development and inflammation [9]. PPAR $\beta/\delta$  is ubiquitously expressed but is expressed at higher levels in the digestive tract and heart. In addition, PPAR $\beta/\delta$  is the predominant isotype in the skin [10]. PPAR $\gamma$  is an established regulator of glucose homeostasis and lipid metabolism [11]. PPAR $\gamma$  also plays an anti-inflammatory role [12]. PPAR $\gamma$  has two different protein isoforms, namely, PPAR $\gamma$ 1 and PPAR $\gamma$ 2 [7]. PPAR $\gamma$ 1 is expressed in many different tissues and inflammatory cells, including macrophages, lymphocytes and dendritic cells. PPAR $\gamma$ 2 is mainly expressed in adipocytes [13]. PPAR $\gamma$  is extensively expressed in immune cells and inhibits inflammatory processes [14]. PPAR $\gamma$  can inhibit the activation and function of macrophages and dendritic cells [12,15] and mediate the survival, activation and differentiation of T cells [16]. In

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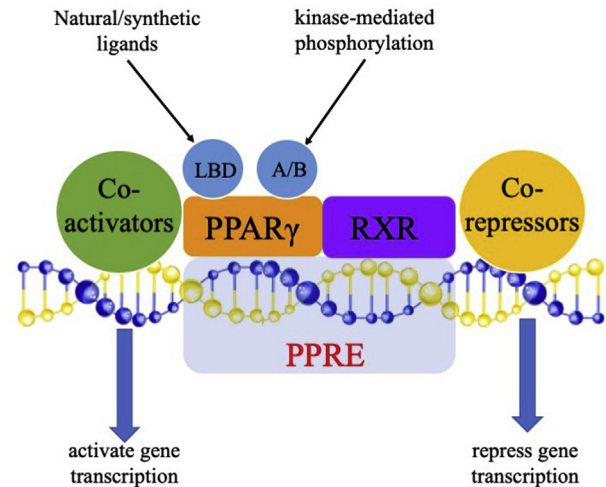
this review, we will summarize the signaling pathways and biological functions of PPAR $\gamma$  and focus on how PPAR $\gamma$  plays a protective role in autoimmune diseases.

## 2. Structure, ligands, and signaling pathways of PPAR $\gamma$

The three-dimensional structure of PPAR $\gamma$  is composed of four domains, including the transactivation and phosphorylation domain (A/B domain), a DNA binding domain (DBD) in the N-terminus, a hinge region, and a ligand-binding domain (LBD) in the C-terminus [17,18]. The A/B domain comprises an activation function 1 region that is required for ligand-independent activation. The DBD is conserved across the nuclear receptor superfamily and functions as a sequence-specific binding site for genomic DNA. The hinge region can modulate the DNA-binding ability and is required for receptor dimerization [19]. The LBD comprises 12  $\alpha$ -helices (H1–H12), leads to heterodimerization with retinoid X receptors (RXRs), and contains an activation function 2 region, which is required for ligation, dimerization, recruitment of coactivators and release of corepressors [20].

Many natural and synthetic compounds can act as ligands of PPAR $\gamma$  [21]. The natural ligands of PPAR $\gamma$ , also known as endogenous agonists, can be divided into four subgroups: (A) the eicosanoid prostaglandin-A1 and the cyclopentenone prostaglandin 15-deoxy- $\Delta^{12,14}$ -Prostaglandin J2 (15D-PGJ2), (B) unsaturated fatty acids, (C) nitroalkanes, and (D) oxidized phospholipids [7]. However, the natural modulators of PPAR $\gamma$  do not always lead to PPAR $\gamma$  activation and target gene transcription [22]. The synthetic ligands of PPAR $\gamma$  are pharmacological agonists and can be divided into 5 subgroups: (I) the thiazolidinedione (TZD) family, including rosiglitazone, pioglitazone and troglitazone, which were the first ligand family developed to bind and activate PPAR $\gamma$  [23], (II) non-TZD agonists, such as cilitazone, netoglitazone and rivoglitazone [24], (III) selective PPAR $\gamma$  modulators (SPPAR $\gamma$ M), which minimize the adverse effects of full PPAR $\gamma$  agonists [25], (IV) dual  $\alpha/\gamma$  agonists [26], and (V) pan  $\alpha/\delta/\gamma$  agonists [27]. These drugs are mainly used to treat type 2 diabetes mellitus [28] (Table 1).

The activation of PPAR $\gamma$  is either ligand-dependent due to the conformational change of the LBD or ligand-independent due to the kinase-mediated phosphorylation of the A/B domain [10]. Primed PPAR $\gamma$  can regulate target gene expression both positively and negatively by binding to specific PPREs in the regulatory sites of these genes [29]. The large Y-shaped ligand binding domain allows PPAR $\gamma$  to recognize many different ligands and to flexibly interact with ligands, which makes it possible for PPAR $\gamma$  to respond to various environmental stimuli and to modulate the expression of target genes [30]. Upon binding to the specific ligand, PPAR $\gamma$  forms a heterodimer with RXR and then translocates to the PPREs of the target genes [31]. This complex can also activate or repress gene transcription directly in a



**Fig. 1. Signaling pathway of PPAR $\gamma$ .** PPAR $\gamma$  can be activated either by its ligands, which bind to the LBD domain, or by the kinase-mediated phosphorylation of its A/B domain. Primed PPAR $\gamma$  can recruit another nuclear receptor, retinoid X receptor (RXR), to form a heterodimer and then bind to the peroxisome proliferator response elements (PPREs) in the promoter regions of the target genes. PPAR $\gamma$  can also recruit coactivator proteins, such as peroxisome proliferator-activated receptor  $\gamma$  coactivator 1 $\alpha$  (PGC-1 $\alpha$ ), or corepressor proteins, such as nuclear receptor corepressor 1 (NCoR1), to activate or repress the transcription of direct target genes in the absence of ligands.

ligand-independent manner through recruitment of coactivator proteins, like peroxisome proliferator-activated receptor  $\gamma$  coactivator 1 $\alpha$  (PGC-1 $\alpha$ ), or corepressor proteins, like nuclear receptor corepressor 1 (NCoR1) [32] (Fig. 1).

## 3. Biological roles and functions of PPAR $\gamma$

PPAR $\gamma$  exhibits multiple functions in cell biology and participates in pathogenesis of metabolism, inflammation and tumor progression. PPAR $\gamma$  has drawn great medical attention as it is a pivotal transcriptional regulator related to glucose and fatty acid metabolism [33]. PPAR $\gamma$  has become a significant target for the treatment of type 2 diabetes [34]. Both isoforms of PPAR $\gamma$  are essential in the regulation of lipid metabolism and insulin sensitivity regulation [35]. Activated PPAR $\gamma$  regulates the expression of genes involved in the release, transportation, and storage of lipids, such as the fatty acid transporter CD36 and lipoprotein lipase [36,37]. PPAR $\gamma$  also promotes balanced and sufficient production of adipocytokines, such as leptin and adiponectin, which modulate insulin function in peripheral tissues [38]. In recent years, PPAR $\gamma$  has been discovered to contribute to the repression

**Table 1**  
The ligands of PPAR $\gamma$ .

Ligands of PPAR $\gamma$	Examples	Effects	References
Natural ligands	the eicosanoid prostaglandin-A1 and the cyclopentenone prostaglandin 15-deoxy- $\Delta^{12,14}$ -Prostaglandin J2(15D-PGJ2)	rapid expression and ability to contribute to a natural defense mechanism	[147]
	unsaturated fatty acids	Upregulate PPAR $\gamma$ expression	[148]
	Nitrated fatty acids (NFAs)	anti-inflammatory and anti-fibrotic effects via PPAR $\gamma$ activation	[149]
	Nitroalkenes	activate PPAR $\gamma$ in monocytes and upregulate FABP4 expression	[150]
Synthetic ligands	oxidized phospholipids	dual effect on bile acid-induced CCL2 expression in pancreatic acini	[151]
	the thiazolidinedione (TZD) family	treatment of type 2 diabetes mellitus	[28]
	the non-TZD agonists	treatment of type 2 diabetes mellitus	[28]
	the selective PPAR $\gamma$ modulators (SPPAR $\gamma$ M)	mediate Tissue-Dependent PPAR $\gamma$ activation and insulin sensitization	[152]
	the dual $\alpha/\gamma$ agonists	treatment of type 2 diabetes mellitus	[28]
pan $\alpha/\delta/\gamma$ agonists	treatment of type 2 diabetes mellitus	[28]	

of proinflammatory genes, such as NF- $\kappa$ B [39]. PPAR $\gamma$  also exerts anti-inflammatory effects through inhibiting the expression of a multitude of pro-inflammatory cytokines and chemokines including interleukin (IL)-1 $\alpha$ , IL-2, IL-6, IL-12, tumor necrosis factor (TNF)- $\alpha$ , interferon (IFN)- $\gamma$ , transforming growth factor (TGF)- $\beta$ , chemokine (C-X-C motif) receptor (CXCR)3 and chemokine (C-X-C motif) ligand (CXCL)9 [40,41]. Via regulating TGF- $\beta$ /Smad signaling pathway, PPAR $\gamma$  exhibits anti-fibrosis property [42]. The activation of PPAR $\gamma$  has also been suggested to regulate microRNA expression to inhibit inflammatory responses. PPAR $\gamma$  could upregulate microRNA (miR)-124 in vitro and in vivo to inhibit the production of pro-inflammatory cytokines [43], and it could enhance the expression of miR-142-3p in vitro and in vivo to inhibit the expression of the pro-inflammatory mediator high mobility group box-1 (HMGB1) which level is increased in multiple autoimmune diseases [44]. In addition, PPAR $\gamma$  can restrain the translocation of HMGB1 through upregulation of protein deacetylase Sirt1 [45]. PPAR $\gamma$  can modulate macrophage and dendritic cell responses and phenotypes, thus ameliorating inflammation [46–49]. Mice bearing macrophage-specific PPAR $\gamma$  ablation develop autoimmune kidney disease and show deficiencies in phagocytosis and clearance of debris from apoptotic cells which leads to the loss of immune-tolerance [50]. Activation of PPAR $\gamma$  can induce the polarization of macrophages towards an immune-modulatory M2-like phenotype and reduce neutrophil migration [51]. PPAR $\gamma$  also alters the T helper (Th)1/Th2 and Th17/regulatory T cells (Treg) ratios. PPAR $\gamma$  can induce the differentiation of Treg cells and suppress the Th17 cells [52]. Mice with T cell-specific PPAR $\gamma$  ablation showed a skewed balance towards Th2 and Treg cells [51]. Microglia plays a critical role in the neuroinflammation and are categorized into classical (M1) and alternative (M2) phenotypes. Pioglitazone can mediate microglia to differentiate into the anti-inflammatory M2 subset which exerts protective effects in neuroinflammation [53]. Due to the anti-inflammatory capacity of PPAR $\gamma$ , Pasquinelli G et al. suggest that agonists of PPAR $\gamma$  may be candidates to prevent or treat the cytokine storm in the COVID-19 disease [54]. Moreover, PPAR $\gamma$  also take part in the regulation of cancer development [55]. PPAR $\gamma$  is downregulated in most, but not all, cancers [56]. Activated PPAR $\gamma$  can suppress tumor progression via the inhibition of some signaling pathways, such as the WNT/ $\beta$ -catenin, PI3K/Akt, signal transducer and activator of transcription (STAT) and nuclear transcription factor- $\kappa$ B (NF- $\kappa$ B) pathways, and the regulation of certain key circadian genes, like brain and muscle aryl-hydrocarbon receptor nuclear translocator-like 1 (Bmal1) [56–58]. However, due to its anti-inflammatory effects, the role of PPAR $\gamma$  in autoimmune diseases has attracted great interest and has been studied by many researchers in recent years (Fig. 2).

#### 4. The roles of PPAR $\gamma$ and PPAR $\gamma$ agonists in autoimmune diseases

##### 4.1. PPAR $\gamma$ and PPAR $\gamma$ agonists in autoimmune thyroid diseases

Autoimmune thyroid diseases (AITDs), for example Graves' disease (GD) and Hashimoto's thyroiditis (HT), are a group of thyroid diseases that are characterized by the autoimmune-mediated damage of thyroid tissues [59]. The prevalence rate of AITD is more than 5% in the general population, but elevated levels of IgG anti-thyroid autoantibodies (AABs) are detected in more than 10% of the general population [60]. The PPAR $\gamma$  expression level increased significantly in adipose or connective tissues from Graves' ophthalmopathy (GO) patients of the active stage compared to normal controls [61]. In vitro experiments demonstrated that PPAR $\gamma$  expression was significantly upregulated in TNF- $\alpha$ -treated GO myoblasts but not in non-GO myoblasts. When treated with pioglitazone, which is a PPAR $\gamma$  agonist, the expression of TNF- $\alpha$ -induced TGF- $\beta$ , hyaluronan (HA), and HAS3 was substantially diminished in myoblasts isolated from patients with GO, which demonstrated PPAR $\gamma$  agonists to be a promising treatment of GO [62]. Moreover, a recent study demonstrated that caffeine may contribute to the prevention of GO by inhibiting the expression level of PPAR $\gamma$ , C/EBP $\alpha$ , and

C/EBP $\beta$  [63]. The anti-inflammatory role of PPAR $\gamma$  in thyroid autoimmunity has also been indicated through modulation of proinflammatory cytokines and chemokines. IFN $\gamma$ -dependent chemokines, such as CXCL9-11, and CXCR3 participate in the development of AITD [64]. These chemokines can induce Th1 lymphocytes to migrate into thyroid tissues to secrete more TNF- $\alpha$  and IFN- $\gamma$ , which in turn stimulate the production of these chemokines and inhibit the expression of PPAR- $\gamma$ , thus perpetuating the inflammatory cascade [65]. In vitro studies have demonstrated that PPAR- $\gamma$  agonists exert an inhibitory effect on the regulation of the chemokines CXCR3 and CXCL9 in the endothelial cells, and CXCL10 and CXCL11 in the thyrocytes [66–68]. The pathogenesis of PPAR $\gamma$  involved in the development of AITD has been summarized in Fig. 3. And the protective roles of PPAR $\gamma$  and its agonists in AITDs are summarized in Table 2.

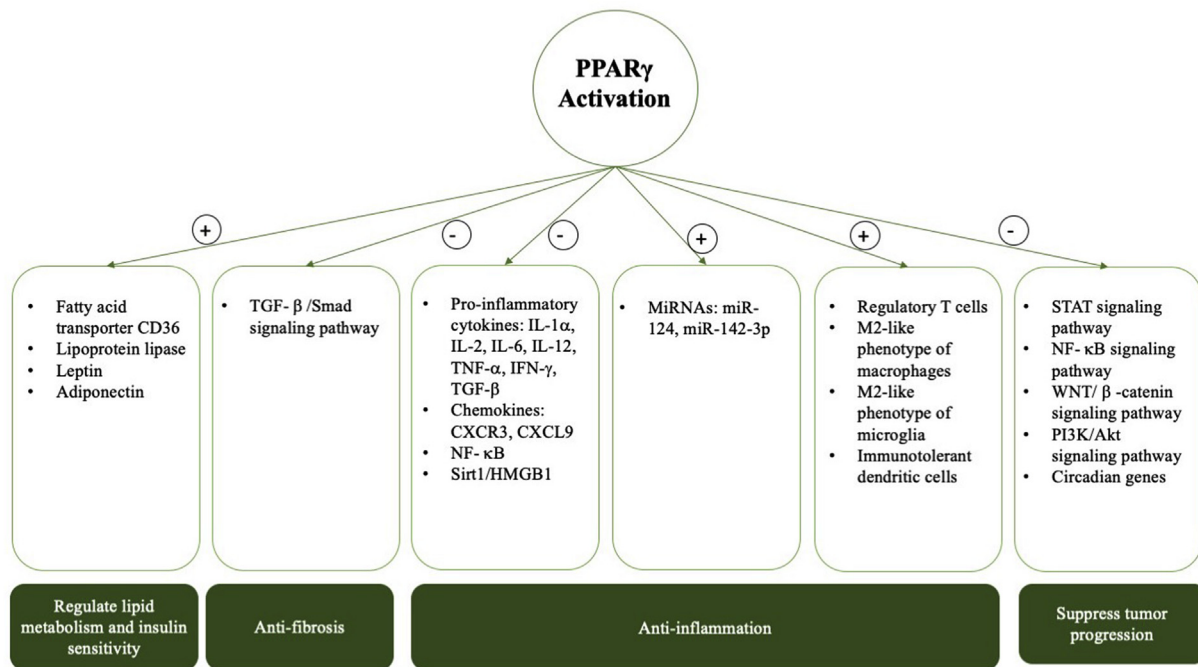
##### 4.2. PPAR $\gamma$ and PPAR $\gamma$ agonists in multiple sclerosis

Multiple sclerosis (MS) is a progressive neurodegenerative disease that is characterized by demyelination of the central nervous system (CNS), immune responses, chronic inflammation, and destruction of the blood-brain barrier [69]. The pathogenesis of MS is not clear, but it may be caused by genetic and environmental factors [70]. During the demyelinating processes in MS, PPAR- $\gamma$  is downregulated [71]. The lack of PPAR- $\gamma$  aggravates the clinical signs in the EAE model [72]. However, PPAR- $\gamma$  can alleviate inflammation and allow remyelination in an MS oligodendrocyte (OL) model [73]. Moringin has been found to have a protective effect in EAE by increasing the level of PPAR- $\gamma$  to inhibit inflammatory factors and can prevent neurodegenerative diseases [74–76]. Ursolic acid is also demonstrated to have a dual effect of anti-inflammation and direct remyelination on the treatment of MS through PPAR $\gamma$ /CREB signaling pathway [77]. Some studies have indicated that PPAR- $\gamma$  agonists can reduce the clinical expression of EAE [78]. Bright et al. demonstrated that more acute EAE could be observed after treatment with PPAR- $\gamma$  antagonists. PPAR- $\gamma$  agonists, such as thiazolidinedione pioglitazone, zigliitazone and the nonthiazolidinedione PPAR- $\gamma$  agonist GW347845, can reduce the T cell proliferation and IFN- $\gamma$  and TNF- $\alpha$  production induced by phytohemagglutinin. Interestingly, pretreatment of a PPAR- $\gamma$  agonist could further inhibit T cell proliferation and cytokine secretion. It has also been proven that PPAR- $\gamma$  agonists reduce the bcl2 expression and induce apoptosis in activated T cells [79]. In addition, several studies have shown that continuous stimulation of PPAR- $\gamma$  can prevent the decreased expression of the receptor caused by inflammation. These studies laid the foundation for future application of PPAR- $\gamma$  agonists in the treatment of MS [80]. In both murine CD4<sup>+</sup> T cells and human models, PPAR $\gamma$  agonists decrease Th17 differentiation. In the infiltrating CD4<sup>+</sup> T cells of the central nervous system, the expression of IL-17 is weakened by the over-expression of PPAR $\gamma$ . The anti-inflammatory effect of PPAR $\gamma$  leads to a decrease in the release of inflammatory cytokines and a decrease in the expansion of brain-derived Th1 and Th17 cells and B lymphocytes [71,81]. Treatment with pioglitazone can significantly decrease the secretion of inflammatory cytokines and enhance the number and functions of regulatory T cells [82].

##### 4.3. PPAR $\gamma$ and PPAR $\gamma$ agonists in rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic organ-specific autoimmune disease that is characterized by inflammatory cells infiltrating into the synovium of the joint, resulting in bone and articular cartilage damage [83,84]. In the synovium of RA patients, the abnormal migration, proliferation, and activation of fibroblast-like synoviocytes (FLSs) are observed in the pannus of bone and cartilage [85]. The histological and immunological characteristics of adjuvant arthritis (AA) in rats are similar to those of RA in humans. Marder W et al. found that expression of PPAR- $\gamma$  in the FLSs of RA and AA was significantly decreased compared with that in normal FLSs as shown by in Western blot and





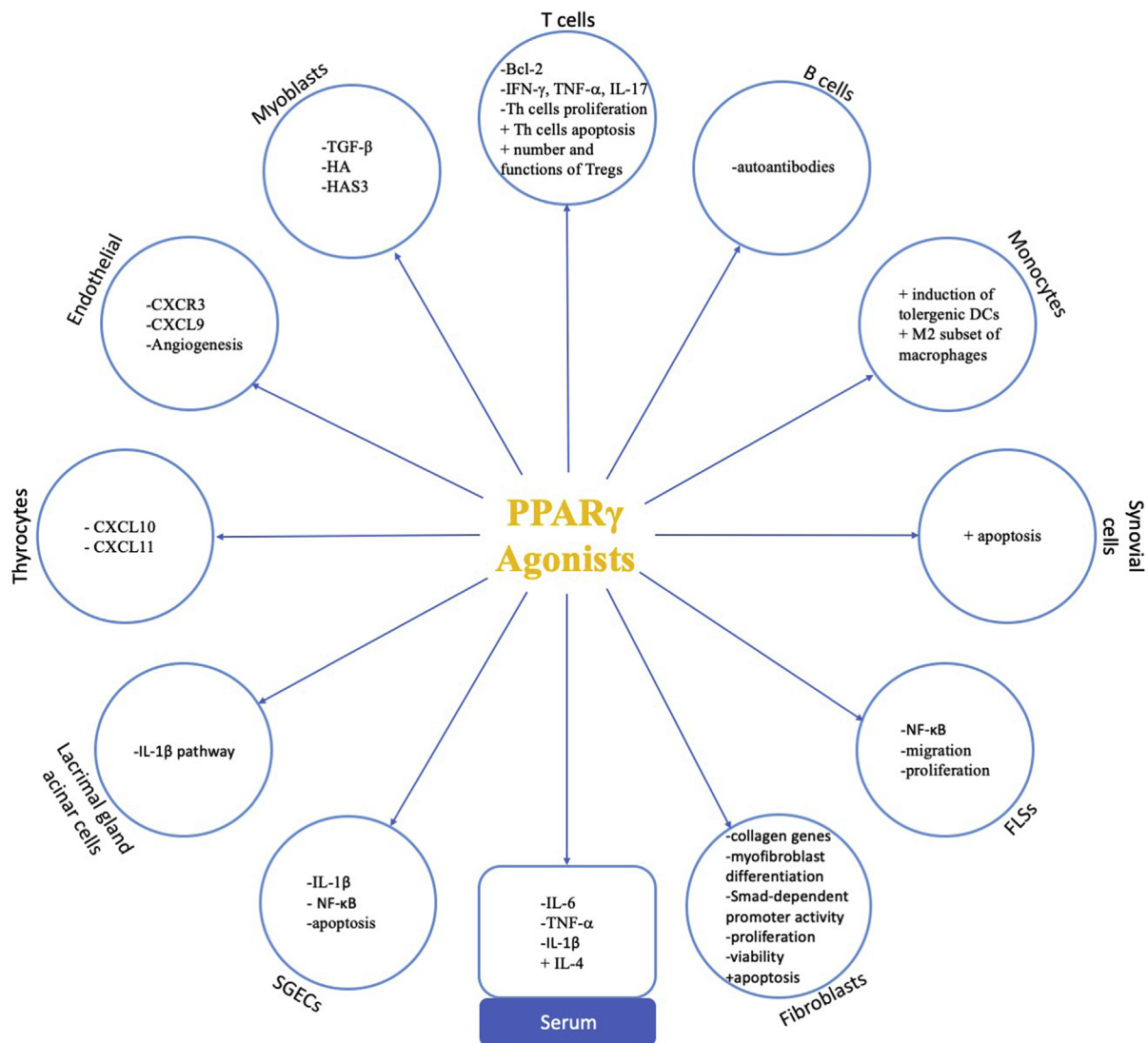
**Fig. 2. Functional roles of PPAR $\gamma$ .** PPAR $\gamma$  is essential in lipid metabolism and control of insulin sensitivity. It is a key transcriptional regulator for fatty acid and glucose metabolism. PPAR $\gamma$  exhibits anti-fibrosis capacity by the inhibition of TGF- $\beta$ /Smad signaling pathway. Activation of PPAR $\gamma$  can also inhibit inflammatory responses through directly repressing genes expression or by regulating microRNAs. PPAR $\gamma$  also participates in the regulation of cancer development via regulating some signaling pathways and circadian genes. Symbols: + enhance, - suppress. Abbreviations: PPAR $\gamma$ , Peroxisome proliferator-activated receptor  $\gamma$ ; HA, hyaluronan; TGF- $\beta$ , transforming growth factor  $\beta$ ; IL, interleukin; TNF- $\alpha$ , tumor necrosis factor  $\alpha$ ; IFN- $\gamma$ , interferon; CXCR, chemokine (C-X-C motif) receptor; CXCL, chemokine (C-X-C motif) ligand; Th, T helper cells; Treg, regulatory T cells; miR, microRNA; HMGB1, high mobility group box-1; Sirt1/Sirtuin1; NF- $\kappa$ B: nuclear transcription factor- $\kappa$ B.

immunohistochemistry [86]. Some assays suggested that the down-regulated PPAR $\gamma$  expression significantly enhanced the migration and proliferation of FLSs in AA rats and normal rats and that the up-regulated PPAR $\gamma$  expression significantly reduced the migration and proliferation of FLSs in AA rats [87]. Moreover, it has been indicated that PPAR $\gamma$  ligands can induce synovial cell apoptosis. NF- $\kappa$ B is a necessary transcription factor for the maintenance of rheumatoid synovitis, and stimulation of FLSs with PPAR $\gamma$  can inhibit the pro-inflammatory activity of NF- $\kappa$ B [88].

The incidence of insulin resistance in patients with rheumatoid arthritis is more than twice as high as that in normal subjects [89], and hyperinsulinemia may aggravate inflammation and is closely related to disease activity [90]. Pioglitazone is a PPAR $\gamma$  agonist. Studies have found that the addition of pioglitazone to RA treatment regimens can alleviate insulin resistance [91]. Pioglitazone has been shown to significantly improve the arthritis index, which is related to the significant decrease in oxidative stress markers and serum cytokines (IL-1 $\beta$  and TNF- $\alpha$ ) [92]. In addition, patients with RA also have vascular dysfunction and an increased augmentation index, which is related to coronary artery atherosclerosis [93]. Pioglitazone can improve certain indexes of vascular function in RA patients, including diastolic blood pressure and the augmentation index, which is not mediated by insulin sensitivity [94]. Besides pioglitazone, another natural PPAR- $\gamma$  agonist, 15d-PGJ2 also modulate bone metabolism through PPAR- $\gamma$  dependent pathways [95]. In addition, some natural agents can also improve arthritis by targeting PPAR- $\gamma$ . The results of a randomized clinical trial revealed that ginger supplementation can upregulate the expression of PPAR- $\gamma$  and ameliorate disease manifestations [96]. And morin, a natural flavonoid, can activate PPAR- $\gamma$  signaling pathway to attenuate synovial angiogenesis [97].

#### 4.4. PPAR $\gamma$ and PPAR $\gamma$ agonists in systemic sclerosis

Systemic sclerosis (SSc) is still a grave disease which is characterized by microvascular dysfunction, autoimmune reactivity and organ fibrosis [98]. Therapies that have been found to be effective in randomized controlled trials (RCTs) are limited, and the advances in treatment observed in other areas have not yet been observed in this field [99]. Fibrosis in multiple organs is the final common pathway in SSc [100]. The underlying mechanism of the uncontrolled progression of fibrosis in SSc remains unclear. However, the impaired PPAR- $\gamma$  expression or function in SSc may partly explain the reason [101]. As early as 2004, researchers demonstrated the expression of PPAR $\gamma$  in normal dermal fibroblasts and found that PPAR $\gamma$  ligation could abrogate the TGF $\beta$ -induced collagen gene expression, inhibit myofibroblast differentiation, and repress Smad-dependent promoter activity of normal fibroblasts [102]. Later, Kohno S et al. found that naturally occurring PPAR $\gamma$  ligands, such as 15-deoxy-Delta(12,14)-prostaglandin J(2), could reduce dermal sclerosis and decrease the expression levels of connective tissue growth factor and TGF $\beta$  in bleomycin-induced scleroderma [103]. Wu M et al. found that the synthetic PPAR $\gamma$  ligand rosiglitazone, which is widely used as an insulin sensitizer, could also attenuate inflammation, dermal fibrosis, and subcutaneous lipotrophy in an animal model of scleroderma [104]. Mice bearing conditional knockout of PPAR $\gamma$  in fibroblast are more susceptible to develop skin fibrosis induced by bleomycin, as indicated by increased dermal thickness and collagen content, and enhanced inflammation and sensitivity of fibroblasts to TGF $\beta$  1 [105]. And mice bearing conditional knockout of PPAR $\gamma$  nuclear corepressor (NCoR) in adipocyte showed significant protection from inflammation and experimental skin fibrosis [106]. All these studies established the role of PPAR $\gamma$  in regulating TGF- $\beta$ -dependent fibrogenesis. Moreover, the unrestrained TGF $\beta$  activity in turn accounted for the markedly diminished expression and impaired function of PPAR- $\gamma$  in SSc [107]. In addition to its effects on



**Fig. 3. Protective roles of PPAR $\gamma$  involved in autoimmune diseases.** Activation of PPAR $\gamma$  can downregulate the expression of CXCL10 and CXCL11 in thyrcytes; decrease the expression of CXCR3 and CXCL9 in endothelial cells and inhibit the angiogenesis process; inhibit TGF- $\beta$ , HA and HAS3 in myoblasts; promote the proliferation and fuction of Tregs and suppress the differentiation and function of Th17 cells, induce apoptosis of Th cells via inhibit the expression of Bcl-2; decrease the production of autoantibodies; promote the differentiation of M2 phenotype of macrophages and the tolergenic DCs; induce the apoptosis of synovial cells; repress the NF- $\kappa$ B signaling pathway in FLSs and inhibit the migration and proliferation of FLSs; suppress the TGF- $\beta$  induced collagen genes expression, the differentiation of myofibroblasts, the Smad-dependent promoter activity in fibroblasts, and inhibit the proliferation and viability of fibroblasts while induce the apoptosis of fibroblasts; suppress the IL-1 $\beta$  and NF- $\kappa$ B signaling pathways in SGECs and inhibit the apoptosis of SGECs; inhibit the IL-1 $\beta$  pathway in lacrimal gland acinar cells; decrease the levels of IL-6, TNF- $\alpha$  and IL-1 $\beta$  while increase the level of IL-4 in the serum. Thus, activation of PPAR $\gamma$  can inhibit the inflammatory reactions, modulate the balance between immune cells and protect the target organs in autoimmune diseases. Symbols: + enhance, - suppress. Abbreviations: PPAR $\gamma$ , Peroxisome proliferator-activated receptor  $\gamma$ ; HA, hyaluronan; TGF- $\beta$ , transforming growth factor  $\beta$ ; IL, interleukin; TNF- $\alpha$ , tumor necrosis factor  $\alpha$ ; IFN- $\gamma$ , interferon  $\gamma$ ; CXCR, chemokine receptor; CXCL, chemokine (C-X-C motif) ligand; Th, T helper cells; Treg, regulatory T cells; miR, microRNA; NF- $\kappa$ B: nuclear transcription factor- $\kappa$ B; FLSs, fibroblast-like synoviocytes; SGECs, salivary gland epithelial cells; DCs, dendritic cells.

fibrogenesis, the activation of PPAR $\gamma$  by rosiglitazone and pioglitazone could also significantly reduce cell proliferation and viability and increase apoptosis of fibroblasts in SSc [108]. Furthermore, PPAR $\gamma$  is also important in the regulation of adipogenesis. In SSc patients and mice treated systemically with bleomycin, PPAR $\gamma$  expression in adipocytes was decreased, and the subcutaneous adipose layer was diminished [109].

In addition to fibrosis, pulmonary arterial hypertension (PAH) is another lethal complication in patients with SSc. Defective PPAR $\gamma$  expression or function also participate in the pathogenesis of PAH [110]. A landmark study reported that both the gene and protein levels of PPAR $\gamma$  were reduced in lung tissue from patients with severe PAH, and the loss of PPAR $\gamma$  expression in their complex vascular lesions led

to angiogenic endothelial cell growth and impaired apoptosis [111]. Mouse experiments also demonstrated the antiproliferative effect of PPAR $\gamma$  in the pathogenesis of PAH. Mice with a targeted deletion of PPAR $\gamma$  in SMCs spontaneously develop PAH [112].

Additional evidence supporting the role of PPAR $\gamma$  in SSc is a genome-wide association study (GWAS) follow-up study, which suggested a possible role for PPAR $\gamma$  in susceptibility to systemic sclerosis [113]. Moreover, a single PPARG intronic SNP (rs10865710) is associated with susceptibility to SSc and PAH [114].

Because of its anti-fibrotic and anti-PAH effects, PPAR $\gamma$  might be a therapeutic target for the control of fibrosis and the pathological vascular remodeling underlying PAH and, therefore, might be a potential drug target for SSc [115]. In recent years, many synthetic agonists of

**Table 2**  
Studies of the protective roles of PPAR $\gamma$  in autoimmune diseases.

Autoimmune diseases	Cell types	Animal models	PPAR $\gamma$ agonists	Effects	Ref
Graves ophthalmopathy (GO)	Myoblasts from extraocular muscles (EOM)		pioglitazone	Diminish the expression of TNF- $\alpha$ -induced TGF- $\beta$ , hyaluronan (HA), and HAS3	[62]
Autoimmune thyroid diseases	thyrocytes		Pioglitazone and RGZ	Inhibit the expression and secretion of the chemokines CXCL10 and CXCL11	[66,67]
Multiple sclerosis	myofibroblast		thiazolidinedione pioglitazone, zigliitazone and nonthiazolidinedione PPAR- $\gamma$ agonist GW347845	Reduce the T cell proliferation and production of the cytokines TNF- $\alpha$ and IFN- $\gamma$ induced by phytohemagglutinin	[79]
Rheumatoid arthritis			Pioglitazone	Alleviate insulin resistance	[91]
Systemic sclerosis			Both natural and synthetic agonists	Abrogate the TGF-beta-induced stimulation of collagen synthesis and myofibroblast differentiation.	[102]
		mouse model of bleomycin-induced scleroderma	15-deoxy-Delta (12,14)-prostaglandin J(2)	(1) Reduce dermal sclerosis, hydroxyproline content, and dermal thickness	[103]
		mouse model of bleomycin-induced scleroderma	Rosiglitazone	(2) Downregulate expression of transforming growth factor beta and connective tissue growth factor	[104]
		mouse model of bleomycin-induced scleroderma	Ajulemic acid	Attenuate inflammation, dermal fibrosis, and subcutaneous lipatrophy	[104]
		mouse model of bleomycin-induced scleroderma	triterpenoid CDDO	(1) Prevent experimental bleomycin-induced dermal fibrosis and modestly reduce its progression	[117,118]
		mouse model of bleomycin-induced scleroderma	Pan PPAR agonist IVA337	(2) Counteract the progression of pulmonary fibrosis	[119]
				Attenuate TGF- $\beta$ signaling and dermal fibrosis	[119]
				(1) Decrease extracellular matrix deposition and reduce expression of phosphorylated SMAD2/3-intracellular effector of TGF- $\beta$ 1	[120]
		Mice bearing fibroblast-specific deletion of PPAR $\gamma$		(2) Downregulate several markers of inflammation	[105]
		Mice bearing adipocyte-specific deletion of PPAR $\gamma$ nuclear corepressor (NCoR)		Fibroblast-specific deletion of PPAR $\gamma$ results in enhanced susceptibility to bleomycin-induced skin fibrosis	[106]
		mouse model of bleomycin-induced scleroderma	EHP-101	Adipocyte-specific deletion of PPAR $\gamma$ nuclear corepressor (NCoR) showed protective effects on experimental skin fibrosis and inflammation.	[116]
	SSc fibroblasts		rosiglitazone and pioglitazone	Inhibit the expression of genes involved in the inflammation, vasculogenesis and fibrogenesis.	[108]
	ECV304 cells			Reduce cell proliferation and cell viability and increase apoptosis	[111]
	human THP-1 and SLE patient-derived macrophages	Mice with targeted deletion of PPAR $\gamma$ in SMCs	rosiglitazone and pioglitazone	Lack of PPAR $\gamma$ results in an angiogenic potential	[112]
Systemic lupus erythematosus		MRU- <i>lpr</i> mice deficient in adiponectin	rosiglitazone and pioglitazone	Spontaneously develop PAH	[124,126,127]
	DCs derived from SLE monocytes		Rosiglitazone combined with dexamethasone	(1) Increased PPAR $\gamma$ expression represses the CD40/CD40L signaling pathway	[128]
	macrophages from SLE patients		Pioglitazone	(2) Induce transcriptional repression of various genes involved in T cell responses	[130]
	SJEGC			(3) Reduce the production of autoantibodies	[134]
Sjogren Syndrome	Cultured lacrimal gland acinar cells	nonobese diabetic mice with Sjogren's syndrome		Induce stable autologous tolerogenic dendritic cells	[135]
		MRU/ <i>lpr</i> mice with a PBC-like cholangitis		Induce the M2 phenotype of monocyte-derived macrophages from SLE patients	[136]
Primary biliary cirrhosis			prostaglandin D metabolite 15-deoxy-A (12,14)-prostaglandin J2 (15d-PGJ2)	Inhibit activation of the NF- $\kappa$ B and IL-1 $\beta$ pathways and apoptosis induced by proinflammatory agents	[140]
				Inhibit the IL-1 $\beta$ pathway	[140]

PPAR $\gamma$  have been indicated to be a promising adjuvant in the prevention and treatment of fibrosis in animal experiments, such as cannabinoid derivative EHP-101 [116], synthetic cannabinoid ajulemic acid (Aja) [117,118], 2-cyano-3,12-dioxo-olean-1,9-dien-28-oic acid, synthetic oleanane triterpenoid [119], and IVA337 [120], which is a pan PPAR agonist. However, more work needs to be conducted to advance these drugs into clinical use.

#### 4.5. PPAR $\gamma$ and PPAR $\gamma$ agonists in systemic lupus erythematosus

Systemic lupus erythematosus is a spectrum of autoimmune disease that is characterized by multiple organ dysfunction and abnormalities in several cell types, such as APCs and T and B cells [121]. The production of autoantibodies and pro-inflammatory cytokines plays a crucial role in the pathogenesis of SLE [122]. Although research on the molecular pathogenesis of systemic lupus erythematosus (SLE) has advanced in recent years, treatment of SLE is still a challenge [123]. However, the increased expression of PPAR $\gamma$  may play a protective role in the pathogenesis of SLE [124]. The PPAR $\gamma$  agonists pioglitazone and rosiglitazone are beneficial for the early prevention of systemic lupus erythematosus and the related atherosclerosis in mice [125]. Zhao et al. also found that pioglitazone treatment could transcriptionally regulate various molecules involved in several T cell-related signaling pathways in the PBMCs and particularly in the isolated CD4<sup>+</sup> T cells from lupus patients. Moreover, pioglitazone could induce the differentiation of T regulatory cells and repress the activation and proliferation of effector T cells in lupus [126]. Furthermore, PPAR $\gamma$  agonist rosiglitazone can reduce the production of autoantibodies, prevent atherosclerosis and renal diseases in mice models of systemic lupus erythematosus, which is based on the induction of adiponectin [127]. In addition, rosiglitazone combined with dexamethasone can induce stable tolerogenic dendritic cells (tolDCs) from monocytes derived from SLE patients [128]. Due to the modulatory role of PPAR $\gamma$  in the differentiation of monocytes and monocyte-derived macrophages, both natural and synthetic agents targeted PPAR $\gamma$  could promote the differentiation of monocytes towards a M2 phenotype and improve the outcome of SLE, which may be an adjuvant to the treatment of this complicated autoimmune disease [129,130].

#### 4.6. PPAR $\gamma$ and PPAR $\gamma$ agonists in Sjogren's syndrome and primary biliary cirrhosis

Sjogren's syndrome (SS) is a classic autoimmune disease that is characterized by the infiltration of lymphocytes and destruction of exocrine glands, leading to the loss of secretory function [131]. Salivary and lacrimal glands are predominantly affected, which leads to the disease hallmarks of severe dryness of the eyes and mouth [132]. Salivary gland epithelial cells (SGECs) derived from SS patients exhibit persistent inflammation. Although the etiology and mechanism of SS remain undefined, a variety of pro-inflammatory cytokines, particularly the persistent activated type I interferon system, are crucial to the pathogenesis of SS [133]. PPAR $\gamma$  and its agonists could modulate the activity of the type I interferon system in SS patients. A previous study found that the transcriptional activity, expression level, and anti-inflammatory function of PPAR $\gamma$  were reduced in ductal epithelial cells from SS patients, and this reduced PPAR $\gamma$  activity promoted the cell-autonomous activation of the IL-1 $\beta$  and NF- $\kappa$ B pathways. Moreover, treatment with PPAR $\gamma$  agonists could repress the activity of NF- $\kappa$ B and prevent proinflammatory agents-induced apoptosis in control SGEC lines and exhibited favorable effects on SS-SGEC lines [134]. PPAR $\gamma$  agonists could also inhibit the IL-1 $\beta$  pathway in lacrimal gland acinar cells [135]. Animal experiments also demonstrated the anti-inflammatory function of PPAR $\gamma$  agonists in nonobese diabetic mouse (NOD mouse) models of SS. Compared with the control mice, mice treated with PPAR $\gamma$  agonists show ameliorated histopathological changes in the salivary glands, decreased expression of IL-6 and TNF- $\alpha$ ,

and increased expression of IL-4 in the serum, which indicated the modulatory role of PPAR $\gamma$  in the balance between Th1 and Th2 cells [136]. In addition, Stergios Katsiogiannis et al. found that endoplasmic reticulum stress contributed to the pathogenesis of SS; therefore, PPAR agonists may be a potential treatment for SS by upregulating adiponectin to modulate the energy metabolism of SGECs [137].

Primary biliary cirrhosis (PBC) is a chronic and progressive autoimmune disease that is characterized by destruction of small intrahepatic bile ducts, leading to potential cirrhosis [138]. PBC patients with extrahepatic conditions had a 56.1% probability of developing SS [139]. PPAR $\gamma$  and its agonists also exhibit immunomodulatory roles in PBC. Nozaki Y et al. found that a PPAR $\gamma$  ligand, the prostaglandin D metabolite 15-deoxy- $\Delta$  (12,14)-prostaglandin J2 (15d-PGJ2), could attenuate portal inflammation in the lupus-prone mouse model with PBC-like cholangitis [140]. PPAR $\gamma$  ligands have exhibited anti-inflammatory properties in SS and PBC, which may add to the therapeutic options available to patients with SS and/or PBC.

### 5. Clinical implications of PPAR $\gamma$ agonists in autoimmune diseases

Owing to the protective role of PPAR $\gamma$  in the development of autoimmune diseases, the natural ligands of PPAR $\gamma$ , for example 15d-PGJ2, virgin olive oil or ginger, may be recommended as a daily supplement to the diet of patients with autoimmune diseases [96,129]. Synthetic ligands of PPAR $\gamma$  have already been widely prescribed to treat type 2 diabetes mellitus. The thiazolidinedione (TZD) family, including the above mentioned rosiglitazone and pioglitazone, were the first synthetic ligands discovered to activate PPAR $\gamma$  [141]. TZDs can enhance insulin sensitivity and regulate lipid and glucose metabolism [142]. Due to the anti-inflammatory properties of thiazolidinedione derivatives, studies have been conducted to examine their use in the control of autoimmune diseases. It has been proven that PPAR $\gamma$  agonists, particularly rosiglitazone and pioglitazone, can ameliorate inflammatory responses and improve the symptoms of autoimmune diseases in animal experiments and in vitro assays. The data of some randomized controlled clinical studies reported that RA patients received additional pioglitazone showed significant improvement in disease activity, insulin resistance, vascular function and lower C reactive protein (CRP) level with minimal safety issues [143–145]. These results suggest that PPAR $\gamma$  agonists may be used as an adjuvant to the standard therapy of autoimmune diseases, particular for those combined with diabetes, obesity or glycometabolism disorder. PPAR $\gamma$  agonists may also protect the target organs, like cardiovascular system, joints or kidney, in the systemic autoimmune diseases. However, the side effects of TZDs, such as heart failure, sodium retention, peripheral edema, weight gain and hemodilution, may limit the use of TZDs [146]. One of the future direction of studies of PPAR $\gamma$  agonists may be the development of novel agents that target PPAR $\gamma$  with minimal adverse events. To achieve a better understanding of the clinical implications of PPAR $\gamma$  agonists, additional clinical trials need to be conducted.

### 6. Conclusion and future directions

In recent years, autoimmune diseases have attracted increasing attention. Autoimmune diseases are characterized by excessive immune responses that cause damage to and dysfunction of certain organs and tissues. Increasing numbers of experiments have shown that PPAR $\gamma$  and its agonists play many different protective roles in autoimmune diseases, which provides novel therapeutic option of the autoimmune diseases. Pioglitazone and rosiglitazone are commonly used PPAR $\gamma$  agonists with excellent safety, which will provide convenience for future clinical trials. However, the current research cannot clearly explain the mechanisms underlying PPAR $\gamma$  protective roles. Further explorations are needed to identify the specific connection between PPAR $\gamma$  and autoimmune diseases to provide a more comprehensive



understanding of their correlation and a theoretical basis for future clinical application.

### Author contributions

Yu Liu collected data and wrote the manuscript, Jiayu Wang made tables and graphs, Shuangyan Luo and Yi Zhan provided technical support and suggestions, Qianjin Lu critically revised the manuscript and provided suggestions.

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### Declaration of competing interest

There is no conflict of interest to declare.

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