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The roles of PPARγ and its agonists in autoimmune diseases: A comprehensive review

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\textbf{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\textsubscript{α}, PPAR\textsubscript{γ}, and PPAR\textsubscript{β/δ}. PPAR\textsubscript{γ} is an established regulator of glucose homeostasis and lipid metabolism. Recent studies have demonstrated that PPAR\textsubscript{γ} exhibits anti-inflammatory and anti-fibrotic effects in multiple disease models. PPAR\textsubscript{γ} 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\textsubscript{γ} and focus on how PPAR\textsubscript{γ} and its agonists play protective roles in autoimmune diseases, including autoimmune thyroid diseases, multiple sclerosis, rheumatoid arthritis, 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\textsubscript{α}, PPAR\textsubscript{β/δ} and PPAR\textsubscript{γ}, 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\textsubscript{α} was the first PPAR subtype to be cloned. The basic function of PPAR\textsubscript{α} is to regulate the oxidation of fatty acids. PPAR\textsubscript{α} is highly expressed in multiple organs and tissues, particularly in the liver, heart, kidneys, brown adipose tissue and skeletal muscles [8]. PPAR\textsubscript{β/δ} 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\textsubscript{β/δ} is ubiquitously expressed but is expressed at higher levels in the digestive tract and heart. In addition, PPAR\textsubscript{β/δ} is the predominant isotype in the skin [10]. PPAR\textsubscript{γ} is an established regulator of glucose homeostasis and lipid metabolism [11]. PPAR\textsubscript{γ} also plays an anti-inflammatory role [12]. PPAR\textsubscript{γ} has two different protein isoforms, namely, PPAR\textsubscript{γ1} and PPAR\textsubscript{γ2} [7]. PPAR\textsubscript{γ1} is expressed in many different tissues and inflammatory cells, including macrophages, lymphocytes and dendritic cells. PPAR\textsubscript{γ2} is mainly expressed in adipocytes [13]. PPAR\textsubscript{γ} is extensively expressed in immune cells and inhibits inflammatory processes [14]. PPAR\textsubscript{γ} can inhibit the activation and function of macrophages and dendritic cells [12,15] and mediate the survival, activation and differentiation of T cells [16].
this review, we will summarize the signaling pathways and biological functions of PPARγ and focus on how PPARγ plays a protective role in autoimmune diseases.

2. Structure, ligands, and signaling pathways of PPARγ

The three-dimensional structure of PPARγ 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 α-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 PPARγ [21]. The natural ligands of PPARγ, also known as endogenous agonists, can be divided into four subgroups: (A) the eicosanoid prostaglandin-A1 and the cyclopentenone prostaglandin 15-deoxy-Δ12,14-Prostaglandin J2 (15D-PGJ2), (B) unsaturated fatty acids, (C) nitroalkanes, and (D) oxidized phospholipids [7]. However, the natural modulators of PPARγ do not always lead to PPARγ activation and target gene transcription [22]. The synthetic ligands of PPARγ are pharmacological agonists and can be divided into 5 subgroups: (I) the thiazolidinedione (TZD) family, including rosiglitazone, pioglitazone and troglitazone, (II) selective PPARγ agonists [23], (III) selective PPARγ agonists, such as cilitazone, netroglitazone and rivoglitazone [24], (IV) selective PPARγ modulators (SPPARγM), which minimize the adverse effects of full PPARγ agonists [25], (IV) dual α/γ agonists [26], and (V) pan α/β/γ agonists [27]. These drugs are mainly used to treat type 2 diabetes mellitus [28] (Table 1).

The activation of PPARγ 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 PPARγ 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 PPARγ to recognize many different ligands and to flexibly interact with ligands, which makes it possible for PPARγ to respond to various environmental stimuli and to modulate the expression of target genes [30]. Upon binding to the specific ligand, PPARγ 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 ligand-independent manner through recruitment of coactivator proteins, like peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α), or corepressor proteins, like nuclear receptor corepressor 1 (NCoR1), to activate or repress the transcription of direct target genes in the absence of ligands.

3. Biological roles and functions of PPARγ

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

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**Table 1**

| Ligands of PPARγ | Examples | Effects | References |
|------------------|----------|---------|------------|
| Natural ligands  | the eicosanoid prostaglandin-A1 and the cyclopentenone prostaglandin 15-deoxy-Δ12,14-Prostaglandin J2 (15D-PGJ2) | rapid expression and ability to contribute to a natural defense mechanism | [147] |
|                  | unsaturated fatty acids | Upregulate PPARγ expression | [148] |
|                  | Nitroalkanes | anti-inflammatory and anti-fibrotic effects via PPARγ activation | [149] |
|                  | oxidized phospholipids | activate PPARγ in monocytes and upregulate FABP4 expression | [150] |
| Synthetic ligands| the thiazolidinedione (TZD) family | dual effect on bile acid-induced CCL2 expression in pancreatic acini | [151] |
|                  | the non-TZD agonists | treatment of type 2 diabetes mellitus | [28] |
|                  | the selective PPARγ modulators (SPPARγM) | treatment of type 2 diabetes mellitus | [28] |
|                  | the dual α/γ agonists | mediate Tissue-Dependent PPARγ activation and insulin sensitization | [152] |
|                  | pan α/β/γ agonists | treatment of type 2 diabetes mellitus | [28] |

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Fig. 1. Signaling pathway of PPARγ. PPARγ 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 PPARγ 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. PPARγ can also recruit coactivator proteins, such as peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α), 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.
of proinflammatory genes, such as NF-κB [39]. PPARγ also exerts anti-inflammatory effects through inhibiting the expression of a multitude of pro-inflammatory cytokines and chemokines including interleukin (IL)-1α, IL-2, IL-6, IL-12, tumor necrosis factor (TNF)-α, interferon (IFN)-γ, transforming growth factor (TGF)-β, chemokine (C-X-C motif) receptor (CXCR)3 and chemokine (C-X-C motif) ligand (CXCL)9 [40,41]. Via regulating TGF-β/Smad signaling pathway, PPARγ exhibits anti-fibrosis property [42]. The activation of PPARγ has also been suggested to regulate microRNA expression to inhibit inflammatory responses. PPARγ 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, PPARγ can restrain the translocation of HMGB1 through upregulation of protein deacetylase Sirt1 [45]. PPARγ can modulate macrophage and dendritic cell responses and phenotypes, thus ameliorating inflammation [46-49]. Mice bearing macrophage-specific PPARγ 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 PPARγ can induce the polarization of macrophages towards an immune-modulatory M2-like phenotype and reduce neutrophil migration [51]. PPARγ also alters the T helper (Th)1/Th2 and Th17/ regulators T cells (Treg) ratios. PPARγ can induce the differentiation of Treg cells and suppress the Th17 cells [52]. Mice with T cell-specific PPARγ 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 PPARγ, Passquinielli G et al. suggest that agonists of PPARγ may be candidates to prevent or treat the cytokine storm in the COVID-19 disease [54]. Moreover, PPARγ also take part in the regulation of cancer development [55]. PPARγ is downregulated in most, but not all, cancers [56]. Activated PPARγ can suppress tumor progression via the inhibition of some signaling pathways, such as the WNT/β-catenin, PI3K/Akt, signal transducer and activator of transcription (STAT) and nuclear transcription factor-κB (NF-κB) 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 PPARγ in autoimmune diseases has attracted great interest and has been studied by many researchers in recent years (Fig. 2).

4. The roles of PPARγ and PPARγ agonists in autoimmune diseases

4.1. PPARγ and PPARγ 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 (AAb) are detected in more than 10% of the general population [60]. The PPARγ 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 PPARγ expression was significantly upregulated in TNF-α-treated GO myoblasts but not in non-GO myoblasts. When treated with pioglitazone, which is a PPARγ agonist, the expression of TNF-α-induced TGF-β, hyaluronan (HA), and HAS3 was substantially diminished in myoblasts isolated from patients with GO, which demonstrated PPARγ 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 PPARγ, C/EBPα, and C/EBPβ [63]. The anti-inflammatory role of PPARγ in thyroid autoimmunity has also been indicated through modulation of proinflammatory cytokines and chemokines, IFN-γ-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-α and IFN-γ, which in turn stimulate the production of these chemokines and inhibit the expression of PPARγ, thus perpetuating the inflammatory cascade [65]. In vitro studies have demonstrated that PPARγ 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 PPARγ involved in the development of AIDs has been summarized in Fig. 3. And the protective roles of PPARγ and its agonists in AIDs are summarized in Table 2.

4.2. PPARγ and PPARγ 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, PPARγ is downregulated [71]. The lack of PPARγ aggravates the clinical signs in the EAE model [72]. However, PPARγ 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 PPARγ 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 PPARγ/CREB signaling pathway [77]. Some studies have indicated that PPARγ agonists can reduce the clinical expression of EAE [78]. Bright et al. demonstrated that more acute EAE could be observed after treatment with PPARγ antagonists. PPARγ agonists, such as thiazolidinedione pioglitazone, zilizilazone and the nonthiazolidinedione PPARγ agonist GW347845, can reduce the T cell proliferation and IFN-γ and TNF-α production induced by phytohemagglutinin. Interestingly, pretreatment of a PPARγ agonist could further inhibit T cell proliferation and cytokine secretion. It has also been proven that PPARγ agonists reduce the bcl2 expression and induce apoptosis in activated T cells [79]. In addition, several studies have shown that continuous stimulation of PPARγ can prevent the decreased expression of the receptor caused by inflammation. These studies laid the foundation for future application of PPARγ agonists in the treatment of MS [80]. In both murine CD4+ T cells and human models, PPARγ agonists decrease Th17 differentiation. In the infiltrating CD4+ T cells of the central nervous system, the expression of IL-17 is weakened by the overexpression of PPARγ. The anti-inflammatory effect of PPARγ 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. PPARγ and PPARγ 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 PPARγ in the FLSs of RA and AA was significantly decreased compared with that in normal FLSs as shown by in Western blot and
Some assays suggested that the down-regulated PPARγ expression significantly enhanced the migration and proliferation of FLSs in AA rats and normal rats and that the upregulated PPARγ expression significantly reduced the migration and proliferation of FLSs in AA rats [87]. Moreover, it has been indicated that PPARγ ligands can induce synovial cell apoptosis. NF-κB is a necessary transcription factor for the maintenance of rheumatoid synovitis, and stimulation of FLSs with PPARγ can inhibit the pro-inflammatory activity of NF-κB [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 PPARγ agonist, and the addition of pioglitazone to RA treatment regimens can decrease in oxidative stress markers and serum cytokines (IL-1β) and TNF-α [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-1β and TNF-α) [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-γ agonist, 15d-PGJ2 also modulate bone metabolism through PPAR-γ dependent pathways [95]. In addition, some natural agents can also improve arthritis by targeting PPAR-γ. The results of a randomized clinical trial revealed that ginger supplementation can upregulate the expression of PPAR-γ and ameliorate disease manifestations [96]. And morin, a natural flavonoid, can activate PPAR-γ signaling pathway to attenuate synovial angiogenesis [97].

4.4. PPARγ and PPARγ 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-γ expression or function in SSc may partly explain the reason [101]. As early as 2004, researchers demonstrated the expression of PPARγ in normal dermal fibroblasts and found that PPARγ ligation could abrogate the TGFβ-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 PPARγ 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 TGFβ in bleomycin-induced scleroderma [103]. Wu M et al. found that the synthetic PPARγ ligand rosiglitazone, which is widely used as an insulin sensitizer, could also attenuate inflammation, dermal fibrosis, and subcutaneous lipatrophy in an animal model of scleroderma [104]. Mice bearing conditional knockout of PPARγ 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 TGFβ1 [105]. And mice bearing conditional knockout of PPARγ nuclear corepressor (NCoR) in adipocytes showed significant protection from inflammation and experimental skin fibrosis [106]. All these studies established the role of PPARγ in regulating TGF-β-dependent fibrogenesis. Moreover, the unrestrained TGFβ activity in turn accounted for the markedly diminished expression and impaired function of PPAR-γ in SSc [107]. In addition to its effects on...
fibrogenesis, the activation of PPARγ by rosiglitazone and pioglitazone could also significantly reduce cell proliferation and viability and increase apoptosis of fibroblasts in SSc [108]. Furthermore, PPARγ is also important in the regulation of adipogenesis. In SSc patients and mice treated systemically with bleomycin, PPARγ 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-γ expression or function also participates in the pathogenesis of PAH [110]. A landmark study reported that both the gene and protein levels of PPARγ were reduced in lung tissue from patients with severe PAH, and the loss of PPARγ expression in their complex vascular lesions led to angiogenic endothelial cell growth and impaired apoptosis [111]. Mouse experiments also demonstrated the antiproliferative effect of PPARγ in the pathogenesis of PAH. Mice with a targeted deletion of PPARγ in SMCs spontaneously develop PAH [112].

Additional evidence supporting the role of PPARγ in SSc is a genome-wide association study (GWAS) follow-up study, which suggested a possible role for PPARγ 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, PPARγ 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...
| Autoimmune diseases                  | Cell types                        | Animal models                                      | PPARγ agonists            | Effects                                                                                           | Ref       |
|--------------------------------------|-----------------------------------|---------------------------------------------------|---------------------------|---------------------------------------------------------------------------------------------------|-----------|
| Graves ophthalmopathy (GO)           | Myoblasts from extraocular muscles (EOM) |                                                   | pioglitazone              | Diminish the expression of TNF-α-induced TGF-β, 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                   |                                   |                                                   | thiazolidinedione, pioglitazone, zivoglitazone and nonthiazolidinedione PPAR-γ agonist GW3478/45 | Reduce the T cell proliferation and production of the cytokines TNF-α and IFN-γ induced by thyroglobulin | [79]      |
| Rheumatoid arthritis                 |                                   |                                                   | Pioglitazone              | Alleviate insulin resistance                                                                      | [91]      |
| Systemic sclerosis                   | myofibroblast                      |                                                   | Both natural and synthetic agonists                   | Abrogate the TGF-beta-induced stimulation of collagen synthesis and myofibroblast differentiation. | [102]     |
|                                     |                                   |                                                   | 15-deoxy-Delta (12,14)-prostaglandin J(2)            | (1) Reduce dermal sclerosis, hydroxyproline content, and dermal thickness                        | [103]     |
|                                     |                                   |                                                   |                                                                         | (2) Downregulate several markers of inflammation and fibrosis                                    | [104]     |
|                                     |                                   |                                                   |                                                                         | Mice bearing fibroblast-specific deletion of PPARγ                                              | [105]     |
|                                     |                                   |                                                   |                                                                         | Mice bearing adipocyte-specific deletion of PPARγ nuclear corepressor (NGO)                     | [106]     |
|                                     |                                   |                                                   |                                                                         | Mouse model of bleomycin-induced scleroderma                                                     | [116]     |
|                                     |                                   |                                                   |                                                                         | EHP-101                                                                                           | [119]     |
|                                     |                                   |                                                   |                                                                         | SSc fibroblasts                                                                                   |           |
|                                     |                                   |                                                   |                                                                         | Rosiglitazone and pioglitazone                                                                   |           |
|                                     |                                   |                                                   |                                                                         | Reduce cell proliferation and cell viability and increase apoptosis                               |           |
|                                     |                                   |                                                   |                                                                         | Lack of PPARγ results in an angiogenic potential                                                  |           |
|                                     |                                   |                                                   |                                                                         | Spontaneously develop PAH                                                                           |           |
|                                     |                                   |                                                   |                                                                         | (1) Increased PPARγ expression represses the CD40/CD40L signaling pathway                         | [124,126,127] |
|                                     |                                   |                                                   |                                                                         | (2) Induce transcriptional repression of various genes involved in T cell responses               |           |
|                                     |                                   |                                                   |                                                                         | (3) Reduce the production of autoantibodies                                                       |           |
|                                     |                                   |                                                   |                                                                         | Induce stable autologous tolerogenic dendritic cells                                             |           |
|                                     |                                   |                                                   |                                                                         | Induce the M2 phenotype of monocyte-derived macrophages from SLE patients                         |           |
|                                     |                                   |                                                   |                                                                         | Inhibit activation of the NF-κB and IL-1β pathways and apoptosis induced by proinflammatory agents |           |
|                                     |                                   |                                                   |                                                                         | Inhibit the IL-1β pathway                                                                           |           |
|                                     |                                   |                                                   |                                                                         | Ameliorates histopathologic changes in the salivary glands through the reduction in Th1 cytokines  |           |
|                                     |                                   |                                                   |                                                                         | Reduce portal inflammation and T cell numbers in portal tracts                                   |           |

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PPARγ 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 oleanene 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. PPARγ and PPARγ 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 PPARγ may play a protective role in the pathogenesis of SLE [124]. The PPARγ 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 transcriptional regulate various molecules involved in several T cell-related signaling pathways in the PBMCs and particularly in the isolated CD4⁺ 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, PPARγ 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 PPARγ in the differentiation of monocytes and monocyte-derived macrophages, both natural and synthetic agents targeted PPARγ 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. PPARγ and PPARγ agonists in Sjögren’s syndrome and primary biliary cirrhosis

Sjögren’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]. PPARγ 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 PPARγ were reduced in ductal epithelial cells from SS patients, and this reduced PPARγ activity promoted the cell-autonomous activation of the IL-1β and NF-κB pathways. Moreover, treatment with PPARγ agonists could repress the activity of NF-κB and prevent proinflammatory agents-induced apoptosis in control SGEC lines and exhibited favorable effects on SS-SGEC lines [134]. PPARγ agonists could also inhibit the IL-1β pathway in lacrimal gland acinar cells [135]. Animal experiments also demonstrated the anti-inflammatory function of PPARγ agonists in nonobese diabetic mouse (NOD mouse) models of SS. Compared with the control mice, mice treated with PPARγ agonists show ameliorated histopathological changes in the salivary glands, decreased expression of IL-6 and TNF-α, and increased expression of IL-4 in the serum, which indicated the modulatory role of PPAR-γ in the balance between Th1 and Th2 cells [136]. In addition, Stergios Katsiougiannis 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]. PPARγ and its agonists also exhibit immunomodulatory roles in PBC. Nozaki Y et al. found that a PPARγ ligand, the prostaglandin D metabolite 15-deoxy-D(12,14)-prostaglandin J2 (15d-PGJ2), could attenuate portal inflammation in the lupus-prone mouse model with PBC-like cholangitis [140]. PPARγ 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 PPARγ agonists in autoimmune diseases

Owing to the protective role of PPARγ in the development of autoimmune diseases, the natural ligands of PPARγ, 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 PPARγ 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 PPARγ [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 PPARγ 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 PPARγ agonists may be used as an adjuvant to the standard therapy of autoimmune diseases, particular for those combined with diabetes, obesity or glycometabolism disorder. PPARγ 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 PPARγ agonists may be the development of novel agents that target PPARγ with minimal adverse events. To achieve a better understanding of the clinical implications of PPARγ 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-γ 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-γ agonists with excellent safety, which will provide convenience for future clinical trials. However, the current research cannot clearly explain the mechanisms underlying PPAR-γ protective roles. Further explorations are needed to identify the specific connection between PPAR-γ 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 Zhang 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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