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Review Article

PPARγ Agonists in Adaptive Immunity: What Do Immune Disorders and Their Models Have to Tell Us?

Laurindo Ferreira da Rocha Junior,[1,2] Andréa Tavares Dantas,[1,2] Ângela Luzia Branco Pinto Duarte,[1] Moacyr Jesus Barreto de Melo Rego,[2] Ivan da Rocha Pitta,[2] and Maira Galdino da Rocha Pitta[2]

[1] *Serviço de Reumatologia do Hospital das Clínicas da Universidade Federal de Pernambuco (HC-UFPE), Recife 50670-901, PE, Brazil*
[2] *Laboratório de Imunomodulação e Novas Abordagens Terapêuticas (LINAT), Núcleo de Pesquisa em Inovação Terapêutica (NUPIT SG), Universidade Federal de Pernambuco (UFPE), Recife 50670-901, PE, Brazil*

Correspondence should be addressed to Laurindo Ferreira da Rocha Junior; laurindorochajr@gmail.com

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Adaptive immunity has evolved as a very powerful and highly specialized tool of host defense. Its classical protagonists are lymphocytes of the T- and B-cell lineage. Cytokines and chemokines play a key role as effector mechanisms of the adaptive immunity. Some autoimmune and inflammatory diseases are caused by disturbance of the adaptive immune system. Recent advances in understanding the pathogenesis of autoimmune diseases have led to research on new molecular and therapeutic targets. PPARγ are members of the nuclear receptor superfamily and are transcription factors involved in lipid metabolism as well as innate and adaptive immunity. PPARγ is activated by synthetic and endogenous ligands. Previous studies have shown that PPAR agonists regulate T-cell survival, activation and T helper cell differentiation into effector subsets: Th1, Th2, Th17, and Tregs. PPARγ has also been associated with B cells. The present review addresses these issues by placing PPARγ agonists in the context of adaptive immune responses and the relation of the activation of these receptors with the expression of cytokines involved in adaptive immunity.

1. Introduction

Adaptive immunity is a very powerful and specialized tool of host defense. The T- and B-cell lymphocytes are classically involved in the adaptive immune system. Disturbances of the adaptive immunity results in autoimmunity. Immune dysfunction associated with autoimmune diseases was known to be caused by an imbalance between Th1 and Th2 cells. Autoimmune diseases could be categorized as predominantly Th1-driven if the major events were cell mediated in nature, or predominantly Th2 driven if antibodies and/or immune complexes served as the main mediators [1]. In the last years, a third subset named Th17 cells has been identified, and the Th1/Th2 imbalance hypothesis has shifted to an involvement of the Th1/Th2/Th17/regulatory T (Treg) lymphocytes with the same Th precursor cells [2]. B-cell activation and antibody production can be either an independent T-cell help process or B cells receiving help from follicular T cells. In autoimmune diseases, the contact with self-antigen leads to B-cell activation and, therefore, these lineage of cells are of great importance in adaptive immunity. Naive B cells develop into antibody-producing plasma cells through the contact with antigen in combination with TLR-agonists and cytokines. Activation of B cells also results in differentiation into plasma blasts and increased cytokine production [3].

The nuclear receptor (NR) superfamily is composed of 48 members and includes receptors for steroid hormones, thyroid hormone, various lipids, and oxysterols. NRs function as ligand-dependent transcription factors and share a modular domain structure [4]. PPAR-gamma (PPARγ) belongs to the nuclear receptor superfamily. These transcription factors function as receptors for various lipid-soluble, small molecules that are most commonly generated as hormones or in the intermediary metabolic pathways [5]. These receptors regulate gene expression upon heterodimerization with the retinoid X receptor by ligating to peroxisome proliferator response elements (PPREs) in the promoter region of target genes. These genes are regulated through ligand-dependent transcriptional activation. Several of these target genes are involved in metabolic homeostasis [6]. The PPARγ express two isoforms, PPAR-γ1 and PPAR-γ2. PPAR-γ1 is expressed in macrophages, colonic epithelial cells, endothelial cells, and vascular smooth muscle cells. PPAR-γ2 is mainly expressed in adipose tissue and is involved in the regulation of adipogenesis [7]. PPARγ activation in immune cells predominantly results in another mechanism of action: transrepression of proinflammatory gene expression [8]. Transrepression does not involve binding of the nuclear receptor to its cognate DNA element, but here PPARγ operates by antagonizing signal-dependent activation of its target genes by other classes of transcription factors, including NF-κB and AP-1 proteins, thereby reducing inflammatory signaling pathways [9]. PPARγ expression in the monocyte/macrophage lineage was demonstrated by the suppression of the activation of monocyte/macrophages by PPARγ agonists. In Addition to their role in the anti-inflammatory response of innate immune cells, PPARs are involved in mediating the adaptive immune responses of T and B cells [10]. PPARγ is activated by diverse synthetic and naturally occurring substances. Many ligands that activate and modulate PPAR functions have been identified [10]. Naïve and activated T cells express PPARγ, and ligands for the receptor inhibit proliferation and significantly decrease cell viability [11]. Activated B cells upregulate their expression of PPARγ [12]. In this review, we will summarize the recent progress in PPARγ studies and the interplay of these nuclear receptors with adaptive immunity and T and B cells.

2. Th1 Lymphocytes

Th1 cells secrete interferon- (IFN-) γ, interleukin- (IL-) 2, and tumor necrosis factor (TNF) and control protection against infection with intracellular microbes. Maturation of Th1 cells is controlled by IL-12 and transcription factor T-bet. During Th1 cell differentiation, IL-12 signals via the IL-12R/STAT4-signalling pathway inducing IFN-γ expression, the secreted IFN-γ then signals through the IFN-γR/STAT1 pathway to further increase IFN-γ levels, forming a positive autoregulatory loop reinforcing Th1 differentiation. The signal transducer and activator (STAT) proteins STAT1 and STAT4 induce the expression of the Th1-specific transcription factor T-box expressed in T cells (T-bet) [13]. Inappropriate activation of Th1 cells in response to self-antigen or innocuous antigens leads to autoimmune states as well as to hypersensitive states in which T-cell tolerance to environmental antigens fails [14].

PPARγ agonists have been shown to decrease IL-2 production in activated T cells and thereby to enhance apoptosis. The modulation of T-cell activity is due to inhibition of IL-2 production in T-cell-receptor-stimulated Th cells and due to suppression of Th2 cell differentiation. The endogenous ligand 15-deoxy-Delta12, 14-prostaglandin J2(15d-PGJ2), and the synthetic ligand ciglitazone inhibit IL-2 secretion by T-cell clones in murine cells [6, 15]. High amounts of IL-2 and IFN-γ were detected in the supernatant of antigen stimulated splenocytes from PPARγ+/− mice [16]. Studies demonstrated that lymphocyte-derived IFN-γ interferes with PPARγ ligand regulation of MAPK activation in murine macrophages *in vitro* [17]. PPARγ ligands decreased the level of IFNγ production in splenocytes and T-cell clones isolated from SJL mice [15]. Treatment with pioglitazone changes the helper T-cell balance from Th1 to Th2 in the myocardium of rats with autoimmune myocarditis by upregulating the mRNA of Th2 cytokine IL-4 and by reducing the mRNA level of Th1 cytokine IFN-γ [18]. Pioglitazone also reduced IFN-γ production in a model of experimental autoimmune encephalomyelitis (EAE), the inflammatory demyelinating disease model of multiple sclerosis (MS) [19]. *In vivo* treatment with the PPAR-ligand THR0921 resulted in reduced production of TNF-α, IL-1β, and INF-γ by spleen cells cultured for 48 h with either lipopolysaccharide (LPS) or type II collagen (CII) compared with cells from vehicle-treated collagen-induced arthritis (CIA) mice [20]. PPARγ agonists decrease lupus-related nephritis through decreased IFN-γ and nitric oxide production in MRL/lpr mice *in vivo* [21]. Treatment of diabetic mice with rosiglitazone resulted in a significant decrease in the pancreatic level of TNF-α and IFN-γ compared to untreated diabetic mice [22].

In human cells, it has been demonstrated that nuclear factor of activated T cells (NFAT) is negatively regulated by PPARγ activation with troglitazone and 15d-PGJ2 through blockade of NFAT DNA binding and transcriptional activity and subsequent inhibition IL-2 production [23]. IL-2 protein expression was also downregulated by rosiglitazone [24]. The endogenous PPARγ agonist 13-hydroxyoctadecadienoic acid (13-HODE) downregulated IL-2 production by human peripheral blood T lymphocytes by reducing NFAT and NF-κB binding to the IL-2 promoter [25]. In PBMCs from patients with Hashimoto's thyroiditis (HT) and controls, rosiglitazone reduced IFN-γ expression by CD4+ and CD8+ T lymphocytes in a dose-dependent manner, but the degree of inhibition was significantly greater in healthy subjects than patients with HT. This *in vitro* resistance to immunomodulation might be due to the enhancement of mitogen-activated protein kinase (MAPK) pathway [26]. The CXC chemokines (CXCL9, CXCL10, and CXCL11), inducible by IFN-γ, are proinflammatory molecules with chemoattractant activity for Th1 lymphocytes secreting IFNγ [27]. Rosiglitazone has recently been shown to inhibit IFN-γ and TNF induction of α-chemokine CXCL10 release by cultured thyroid cells and orbital fibroblasts from patients with Graves' ophthalmopathy [28]. Troglitazone has been demonstrated to modulate the level of IFN-γ production [29, 30]. The deletion of PPARγ in CD4+ T cells results in enhanced antigen-specific proliferation and overproduction of IFN-γ in response to IL-12 highlighting the importance of expression of PPARγ in CD4+ T cells in downregulating excessive Th1 responses [31]. 15d-PGJ2 suppressed T-cell proliferation and IFN-γ secretion *in vitro* by both Con A- and myelin basic protein (MBP) Ac1–11 peptide-stimulated lymphocytes. MBP is used to induce EAE in rodents. The ability of T cells to adoptively transfer EAE is suppressed when these cells are cultured with 15d-PGJ2 *in vitro* [32]. 15d-PGJ2 acts cooperatively with 9-*cis* retinoic acid, the ligand for the retinoid X receptor (RXR), in inhibiting microglial cell activation. Microglia participate in pathology associated with multiple sclerosis (MS) [33]. The PPARγ ligands, 15d-PGJ2, troglitazone, and pioglitazone, can inhibit the IFN-γ-induced expression of the CXC chemokines inducing protein-10 and monokine induced by IFN-γ/IFN-inducible T-cell αchemoattractant by endothelial cells [34]. In addition, T-cell-specific PPARγ-deficient mice are suggested to be defective in accumulating T effector cells in secondary lymphoid organs and tissues and therefore in their ability to produce IFN-γ gamma and IL-17 in inflammatory sites [26, 35].

IL-12 plays a crucial role in the differentiation of T lymphocytes and immunity against pathogens. The development of EAE was also found to be associated with an increase in the expression of IL-12 in the central nervous system (CNS) and lymphoid organs [36, 37]. The PPARγ agonists 15d-PGJ2 and ciglitazone inhibit EAE by blocking IL-12 production in macrophage and microglial cells, IL-12 signaling, and Th1 cell differentiation [38, 39]. The endogenous ligand 9-hydroxyoctadecadienoic acid (9-HODE), a major oxidized lipid component of oxLDL, significantly inhibited IL-12 production in lipopolysaccharide- (LPS-) stimulated mouse macrophages and also suppressed NF-κB-mediated activation in IL-12 p40 promoter [40].

The inhibition of IL-12 production by dendritic cells through ligand-activated PPARγ, as well as the inhibition of IFNγ production by T cells, indicates that this nuclear hormone receptor might be involved in the differentiation of naive T cells into their effector subsets. These data highlight that PPARγ play important roles in Th1-cell survival, activation, and differentiation.

3. Th2 Cells

Th2 cells classically mediate host defense against extracellular parasites. They are also important in the induction and persistence of asthma and other allergic inflammatory diseases. Th2 cells can produce IL-4, IL-5, IL-9, IL-10, IL-13, and IL-25. IL-4 plays a positive feedback for Th2 cell differentiation through the transcription factor STAT-6 and expression of GATA-3 [41]. Although Th2 cells are not major effectors in the pathogenesis of most autoimmune diseases, in some instances induction of a Th2 response during ongoing autoimmune inflammation can be of therapeutic value, especially considering the potential of Th2 cells to modulate the generation of Th1 cells and their interactions with B cells. Th2 cytokines can stimulate proliferation, activation, and isotype switching of B cells and aid in the production of autoantibodies by providing help to autoreactive B cells [42, 43]. Futhermore, Th2 cytokines, like IL-5, can promote induction of Ag-specific Tregs, contributing to restore autoimmune tolerance [44].

Studies of gene expression have shown that polarized Th2 cells express greater levels of PPARγ2 mRNA than Th1 cells [45]. The exact interaction between PPARγ and IL-4 is not fully understood, and it seems to depend on the context and on the ligand type involved. Treatment with pioglitazone increased expression levels of IL-4 in a model of autoimmune myocarditis, and there was an amelioration of the inflammation [18]. This report agrees with previous description of improvement of acute colitis after thiazolidinic treatment (troglitazone, pioglitazone, and rosiglitazone) by decreasing TNFα and IFNγ and increasing IL-4, IL-10, and transcription factor GATA-3 expression [46, 47]. Recently, pioglitazone attenuated the neurological signs in a model of experimental autoimmune neuritis in rats by the inhibition of Th1 cytokines production (TNFα and IFNγ) and increased secretion of IL-4 [48]. In PBMC from Hashimoto's thyroiditis patients, rosiglitazone produced no inhibitory effect on IL-4 expression by CD4+ T lymphocytes [26].

On the other hand, significant inhibition of IL-4 production in T cells by natural and synthetic PPARγ agonists (15d-PGJ2 and ciglitazone) was reported [7]. In this study, the inhibitory effect was explained, at least in part, by downregulation of NF-AT (nuclear factor of activated T cells) activation, another proinflammatory signal transduction pathway [7]. This finding was subsequently confirmed by other authors [49, 50]. Furthermore, it was demonstrated that a nonthiazolidinedione PPARγ ligand (KR62980), but not rosiglitazone, decreased IL-4, IL-5, and IL-13 levels and Th2 cell differentiation *in vitro*, by reducing the expression of c-Maf, a Th2-specific transcription factor [51]. These findings suggest that PPARγ activation could have an anti-inflammatory effect on Th2-mediated diseases.

It was also demonstrated that IL-4 and IL-13 could upregulate PPARγ gene expression in CD4+ T cells, peripheral monocytes, peritoneal macrophages, and airway epithelial [52–55]. These authors also showed that IL-4 induces the expression and activity of 12/15-lipoxygenase, enzyme that catalyzes the synthesis of the PPARγ ligands 12-HETE, 15-HETE, and 13-HODE. This finding reinforces the important role of this cytokine in inflammation by coordinately inducing the expression of PPARγ receptor and its ligands and, consequently, proinflammatory gene repression [52, 53].

IL-10 is an anti-inflammatory cytokine that downregulates cellular immunity and allergic inflammation, by inhibiting activation and effector function of T cells, monocytes, and macrophages; downregulating IL-4 and IL-5 expression by T-helper type 2 cell lymphocytes and decreasing eosinophil survival and IgE synthesis [56, 57]. In a mouse model of asthma, the administration of rosiglitazone or pioglitazone increased IL-10 levels in lung tissue and decreased IL-4 and IL-5 levels, indicating a protective role for the receptor in inflammatory diseases [50]. The PPARγ agonists effects seem to depend on dose and cell type, since low concentrations of rosiglitazone induced production of IL-10 from mature dendritic cells and activated CD4+ T cells, but these effects were not identified with higher doses or in immature cells. This production was mediated by PPARγ receptors, and it was also described as a functional PPRE in the IL-10 gene promoter [58].

Some studies have suggested that PPARγ agonists may also have some proinflammatory activity in which 15d-PGJ2 can inhibit IL-10 action by blocking STAT1 and STAT3 activation. This inhibition was not specific for IL-10, as STAT activation by IFNγ or IL-6 is also inhibited by the compound [59]. Thus, some PPARγ ligands can exert their pro- or anti-inflammatory properties through a PPARγ-independent way.

IL-33 can act directly on Th2 cells increasing the secretion of Th2 cytokines such as IL-5 and IL-13 and can also act as a chemoattractant for Th2 cells [60, 61]. It was demonstrated that treatment with PPARγ agonists (15d-PGJ2 and rosiglitazone) could also reduce the production of IL-33, and they have been implicated in the pathogenesis of some inflammatory diseases mediated by eosinophils, like asthma [62].

In addition to downregulating Th1 proinflammatory cytokines, PPARγ ligands can presents anti-inflammatory effects by promoting the production of anti-inflammatory Th2 cytokines. Thus, PPARγ was suggested to modulate the orientation of immune responses in favor of Th2 responses, but the studies are not uniform.

4. Th17 Pathway

Recently, a new subset of Th cells has been identified named TH17 cells and characterized by the production of IL-17A, IL-17F, IL-21, IL-22, and IL-23R. Th17 cell differentiation is enhanced by the coordinated functions of distinct cytokines including TGFβ, IL-6, IL-21, and IL-23, whereas IL-2, IL-4, IFNγ, and IL-27 inhibit its differentiation. The IL-17A and IL-17F induce proinflammatory cytokines like IL-6, IL-1, TNF, and proinflammatory chemokines like CXCL1, GCP-2, and IL-8 and thus promote tissue inflammation and recruitment of neutrophils to the site of inflammation [63]. This cell population has been implicated in the development of autoimmune diseases, such as multiple sclerosis, rheumatoid arthritis, and inflammatory bowel disease and has been studied in mouse models of autoimmunity, such as experimental autoimmune encephalomyelitis, inflammatory bowel disease, and collagen-induced arthritis [64–67]. In several autoimmune diseases, Th17 cells are recruited to inflamed tissues and promote inflammation by enhancing cytokine production, which can in turn activate B-cell antibody production, activate dendritic cells, and stimulate resident cells in the target tissues [57].

Pharmacological PPARγ activation selectively impairs differentiation into Th17 cells. Under physiological conditions, the corepressor SMRT (silencing mediator of retinoid and thyroid hormone receptors) is bound to the RORγt promoter and inhibits its transcription. PPARγ activation is thought to prevent removal of this corepressor complex, thus suppressing RORγt expression and RORγt-induced Th17 cell differentiation [67, 68]. In PPARγ knockout mice (PPARγ−/−), Th17 differentiation was strongly increased. In a model of EAE, characterized by increased infiltration of Th17 cells into the central nervous system, pioglitazone treatment alleviated the disease severity of EAE, and PPARγ−/− mice were reported to exhibit enhanced disease severity. In CD4+ T cells isolated from the central nervous system (CNS) of these EAE mice, endogenous (13-HODE) and synthetic (pioglitazone) PPARγ agonists suppressed Th17 differentiation, but not Th1, Th2, or Treg differentiation. A decreased expression of Th17 cytokines IL-17A, IL-17F, IL-21, IL-22, and IL-23R and a selective inhibition of TGFβ/IL-6-mediated expression of RORγt were also demonstrated [69].

IL-23 belongs to IL-12 cytokine family and represents an important cytokine implicated as being responsible for Th17 phenotype maintaining and survival [70, 71]. PPARγ agonists (15d-PGJ2 and rosiglitazone) inhibited the induction of IL-23 protein by LPS-stimulated CNS cells [72]. In models of allergic asthma, treatment with PPARγ agonists (15d-PGJ2 and rosiglitazone and pioglitazone) promoted the reduction of IL-17 and IL-23 [62, 73]. These studies demonstrate that PPARγ activation can regulate the differentiation and function of Th17 cells, by suppressing Th17 cell development and decreasing Th17 cytokines.

5. T Regulatory (Treg) Cells

Treg cells suppress autoimmune responses and also other aberrant or excessive immune responses to nonself-antigens. Depletion of CD25+CD4+ Treg cells, which constitute 5%–10% of CD4+ T cells, produces autoimmune diseases such as inflammatory bowel disease in normal mice [74]. Expression of PPARγ by macrophages and epithelial cells is required for protection against dextran sodium sulfate colitis [75, 76]. These Treg cells express FoxP3, a transcription factor essential for their development and function [77]. PPARγ-expressing Treg effectively reduce IFN-γ-producing CD4+ T cells. Therefore, the loss of PPARγ in Treg impairs their ability to control effector CD4+ T-cell responses preventing protection against colitis in a mouse model of intestinal inflammation suggesting that expression of PPARγ by Treg is required for optimal anti-inflammatory efficacy [31].

PPARγ deficiency leads to decreased numbers of CD4+Foxp3+ T cells and increased CD4+IFN-γ+ cells, suggesting that PPARγ plays a role in Treg survival and regulation of effector T-cell functions. Similarly, T-cell-specific PPARγ-deficient mice showed reduced Treg recruitment to mesenteric lymph nodes and increased expression of apoptosis-related genes [78]. In addition, ciglitazone or PGE2 treatment of naïve CD4+ T cells enhanced induction of Foxp3+ inducible regulatory T cells, suggesting that PPARγ may contribute to the quality and quantity of Treg functions *in vivo*. PPARγ regulates induction of Tregs through retinoic acid-mediated dendritic cells (DCs) [79, 80].

Foxp3+ Treg cells are abundant in visceral adipose tissue and have a different T-cell receptor repertoire compared with Treg cells in other tissues [81]. These cells specifically express the PPARγ and its stimulation by pioglitazone and increase Treg cell numbers in the visceral adipose tissue [82]. These findings suggest that PPARγ-expressing Treg cells in adipose tissue might control inflammation in obesity, providing a new link between immunoregulation and metabolic disease [83].

6. B Cells

The exact role of B cells in the pathogenesis of autoimmune diseases is still matter of research. One previous hypothesis proposed that autoimmune disease develops as a result of

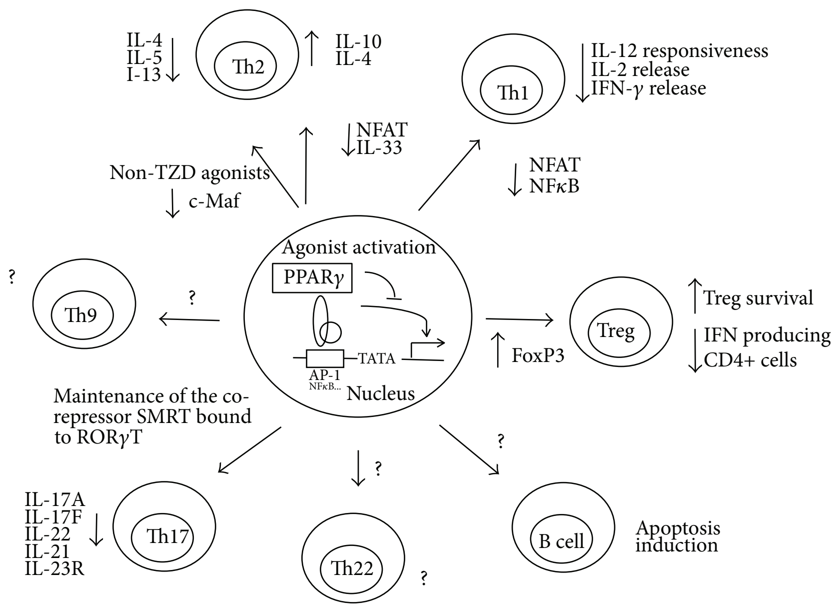

Figure 1: Effects of PPARγ agonists on cytokine expression and on lymphocytes involved in adaptive immunity. ? Represents mechanisms that are not well elucidated.

persistence of self-reactive clones of lymphocytes that should have been deleted via normal immune tolerance, although some had suggested that this could be an epiphenomena. The success of B-cell depletion therapy in autoimmune diseases, particularly in rheumatoid arthritis (RA) [84], systemic lupus erythematosus (SLE) [85], antineutrophil cytoplasmic antibody- (ANCA-) related vasculitides [86], and multiple sclerosis [87], reinforces the importance of B cells in the pathogenesis [88].

Papers discussing the role of PPARγ agonists in B cells focus on the induced apoptosis by natural and synthetic agonists. The PPARγ mRNA and protein expression in mouse B cells is described, and it has been suggested that PPARγ agonists (15d PGJ2) could be involved in the induction of apoptosis in B lymphocytes [89]. The same group demonstrated the nuclear and cytoplasmic expression of PPARγ in normal human B lymphocytes. An antiproliferative effect of natural (15d PGJ2) and synthetic PPARγ ligands (ciglitazone) on human B cells through inducing apoptosis is also shown [90].

On the other hand, PPARγ expression was increased in human activated B cells as compared to nonactivated cells. Using low doses of PPARγ ligands (15-d-PGJ2 and rosiglitazone), they found an increase of B-cell proliferation and IgM and IgG antibody production. These effects were related to activation of the cells: activated B cells, which had higher PPARγ levels, can respond to PPARγ ligands, while nonactivated B cells, with low PPARγ expression, were not able to activate PPARγ upon low-dose PPARγ ligand exposure. There was also a raise of stimulated memory B cells differentiation to plasma cells [12]. In an animal model of asthma, 15d-PGJ2 inhibited LPS-induced B cell proliferation [62], and, in peripheral blood mononuclear cells of atopic dermatitis patients, there was significant inhibition of IgE synthesis [49].

The role of PPARγ in B cells in autoimmune diseases is less well documented. In PPARγ heterozygote knockout mice (PPARγ+/−), in which PPARγ expression is reduced by 50%, B-cell proliferative response was enhanced, but not T cells. Furthermore, PPARγ+/− mice developed more severe antigen-induced arthritis, that was suggested to be due to B-cell hyperreactivity. However, the production of T-cell-derived cytokines was also enhanced, since higher amounts of both IL-2 and IFN-γ were detected in the supernatant of antigen stimulated splenocytes from PPARγ+/− mice, and it was suggested that the alteration in T-cell function caused by reduced PPARγ expression could be responsible for the results [16].

The interaction between T and B cells and the autoantibodies production are key elements in the SLE pathogenesis. Recently, some studies have suggested the PPARγ participation in this complex disease. An increased PPARγ expression in patients with active SLE was described [91]. PPARγ agonist rosiglitazone was shown to reduce autoantibody production and ameliorate renal disease in a murine SLE model [92]. Ciglitazone inhibited IgE production in nonallergic and atopic dermatitis models *in vitro* and *in vivo* [49]. Indeed, these effects are not proven directly mediated by activated B lymphocytes, but rather indirectly mediated via regulatory signal pathways of other cells types. Reduction in PPARγ expression increases T-cell proliferation and skews toward Th1 immune response, which includes increased IFNγ and IL-12 production [16, 38]. These cytokines can directly influence B-cell function, including plasma cell formation, proliferation, and antibodies production [93–95].

7. Perspectives

In conclusion, PPARγ agonists are important modulators of the inflammatory process and lymphocyte homeostasis.

Currently, there is evidence to support that PPARγ is involved in Th lymphocyte differentiation, B lymphocyte effector functions, and cytokine expression. Figure 1 summarizes the effects of PPARγ agonists on cytokine expression and on T regulatory cells and B cells. PPARγ is expressed by the main cell types of adaptive responses. Natural and synthetic PPARγ ligands proved to be capable of inhibiting major signaling pathways of adaptive immunity, reducing or augmenting the expression of cytokines. In fact, PPARγ ligands were shown to inhibit the production of several proinflammatory cytokines. Thus, further studies are necessary to clarify the use of PPARγ antagonists in diseases driven by the Th imbalance such as autoimmune diseases. The actions of these compounds at the cellular levels and their proven immunomodulatory effects make it worth considering their use in clinical trials exploring the possibilities that these drugs might help in the treatment of immune diseases.

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