Review Article

Role of PPARs in Trypanosoma cruzi Infection: Implications for Chagas Disease Therapy

Eugenia Hovsepian,1 Federico Penas,1 Gerardo A. Mirkin,2 and Nora B. Goren1

1 Centro de Estudios Farmacológicos y Botánicos (CEFYBO, CONICET, UBA), Buenos Aires 1121, Argentina
2 Departamento de Microbiología, Parasitología e Inmunología, Facultad de Medicina, Universidad de Buenos Aires, Buenos Aires 1121, Argentina

Correspondence should be addressed to Nora B. Goren, ngoren@fmed.uba.ar

Received 8 September 2011; Accepted 3 November 2011

Academic Editor: Dunne Fong

Copyright © 2012 Eugenia Hovsepian et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Chagas disease, which is caused by Trypanosoma cruzi (T. cruzi), remains a substantial public health concern and an important cause of morbidity and mortality in Latin America. T. cruzi infection causes an intense inflammatory response in diverse tissues by triggering local expression of inflammatory mediators, which results in the upregulation of the levels of cytokines and chemokines, and important cardiac alterations in the host, being one of the most characteristic damages of Chagas disease. Therefore, controlling the inflammatory reaction becomes critical for the control of the proliferation of the parasite and of the evolution of Chagas disease. The nuclear receptors known as peroxisome proliferator-activated receptors (PPARs) have emerged as key regulators of lipid metabolism and inflammation. The precise role of PPAR ligands in T. cruzi infection or in Chagas disease is poorly understood. This review summarizes our knowledge about T. cruzi infection as well as about the activation of PPARs and the potential role of their ligands in the resolution of inflammation, with the aim to address a new pharmacological approach to improve the host health.

1. Introduction

Chagas disease is widely distributed throughout Latin America, thus causing a serious public health problem. It is considered the parasitic disease that leads to the greatest economic burden in Latin America due to its prolonged chronicity. Reasonably, public control programs normally focus their resources and strategies on the elimination of insect vectors associated with human habitat and relegate the infected patient. Moreover, migration from rural to urban areas has changed the epidemiology of the disease. While in the 1930’s 70% of Latin Americans lived in rural areas, currently about 70% live in urban areas. The infection was primarily rural and became urban transmissible by blood transfusion. In recent decades, the number of donors with positive serology has increased in endemic countries. Thus, there is a need for new strategies to prevent or stop the cardiac consequences of T. cruzi infection, with an affordable cost to the health system and patients. The host responds to invasion by the activation of inflammation and induction of innate and specific immunity. The infectious inflammatory myocarditis generated by T. cruzi induces an inflammatory response that affects the heart tissue and function. Moreover, the immune system can act with autoimmune reaction with infiltration of macrophages and/or cell-damaging attack. Therefore, the anti-inflammatory actions of peroxisome proliferator-activated receptors (PPARs) γ and α have received great attention because of the availability of synthetic PPAR activators. PPAR ligands emerge as attractive drug targets for lipid and glucose metabolism as well as for inflammation resolution. The aim of this article is to review the role of PPARs in T. cruzi infection and their potential contribution to inflammation resolution.

2. Chagas Disease

Chagas disease, also called American trypanosomiasis, is a chronic and systemic parasitic infection caused by the protozoan Trypanosoma cruzi. This parasite was discovered
in 1909 by the Brazilian physician Carlos Chagas (1879–1934), who described in detail the cycle of transmission and the human clinical manifestations.

This infectious disease is endemic throughout Central and South America and is still recognized by the World Health Organization (WHO) as one of the most important ignored tropical diseases and as a significant public health problem. In recent decades, the increased rate of emigration from Chagas-endemic countries to the United States, Canada, and the European Union has become a new concern for the WHO [1].

*T. cruzi* has several instances of transmission to humans and other susceptible hosts, mainly through contact with the feces of infected blood-feeding insect vectors. However, alternative routes such as blood transfusion, organ transplant, congenital transmission and oral transmission have also been determined [2].

The clinical course of the infection has two phases: an acute and a chronic. The acute phase is characterized by evident parasitemia and parasitism in a wide variety of host cells. This phase can be confused with other infections since symptoms such as fever or hepatomegaly and/or splenomegaly are shared by different infectious diseases. Most of the patients that survive the acute phase remain in a life-long asymptomatic state (indeterminate form) during the chronic phase of infection [3].

During the acute phase of infection, most individuals usually have mild symptoms such as fever, which do not need medical attention, with few or no parasites found in circulation. Symptoms of acute infection may last up to a few weeks or months. Although the infection then remains largely asymptomatic, often for years or even decades, 30% of patients develop chronic Chagas disease [4].

Symptoms of the acute phase resolve spontaneously in about 90% of infected patients even if the infection is not treated with trypanocidal drugs. About 60–70% of these patients will never develop clinically apparent disease. These patients have the indeterminate form of chronic Chagas disease. The remaining 30–40% of patients will develop a form of chronic disease characterized by progression to cardiac disease, gastrointestinal disease, or both, over a period of years to decades [3, 5, 6].

The cardiomyopathy in South and Central America develops manifestations like cardiac arrhythmias, apical aneurysms, congestive heart failure, thromboembolism, and sudden cardiac death in disease-endemic areas [7]. As expected, Chagas disease can be reactivated in patients with HIV/AIDS or subject to chemotherapy [8].

It has been described that Chagas disease is typified by a chronic inflammatory process that causes damage to the myocardium as well as to the conduction system. The pathogenesis may involve several mechanisms, including immunologically mediated tissue damage, cardiac dysfunction, and coronary microvascular disease [9]. There are substantial evidences showing that cardiac tissue, an important target of *T. cruzi*, produces marked amounts of proinflammatory cytokines, chemokines, and enzymes including inducible nitric oxide (NO) synthase (NOS2) and metalloproteinases (MMPs), resulting in inflammation and cardiac remodeling in response to parasite infection [10–12].

### 3. The Peroxisome Proliferator-Activated Receptors (PPARs) Family

PPARs are members of the nuclear receptor superfamily of ligand-activated transcription factors. The PPAR subfamily (NR1C) includes PPAR-α (NR1C1), PPAR-β (also called PPAR-δ) and NUC1, NR1C2, and PPAR-γ (NR1C3) [13], each with different ligands, target genes, and biological role. Most of these PPARs share a similar structure, which includes an amino-terminal activation domain (AF-1), a DNA-binding domain, a ligand-binding domain, and a second carboxy-terminal activation domain (AF-2) [14]. In response to ligand binding, these receptors change their conformational structure recruiting coactivators and free corepressors. The PPAR family not only regulates metabolic processes but also participates in extrametabolic processes, including direct activation of genes, ligand-independent repression, ligand-dependent repression, and transrepression [15].

Nuclear receptors can be activated by ligand-dependent or -independent mechanisms. PPARs are activated by xenobiotics as well as by endogenous fatty acids and their metabolites. PPARs activate the transcription of their target genes as heterodimers with retinoid X receptors (RXRs), which are activated by 9-cis retinoic acid [16, 17]. Eicosanoids are some of the endogenous ligands that bind to the PPAR-RXR complex, leading to conformational changes, freeing the corepressor, and thus binding to the response element of target genes [15] (Figure 1). PPARs have been cloned in several species, including rodents, amphibians, teleosts, cyclostomes, and even humans. The PPAR subtypes (α, β, and γ) are expressed differently according to the tissue but may also be coexpressed in different relative concentrations [18].

#### 3.1. PPAR-α.

PPAR-α was identified in the early 1990s on the basis of it being a target of hypolipidemic fibrate drugs and other compounds that induce peroxisome proliferation in rodents [19]. PPAR-α is expressed in cells that have active fatty acid oxidation like hepatocytes, cardiomyocytes, enterocytes, smooth muscle cells, and kidney cells and has been implicated in the regulation of cellular energetic processes. It has been shown that PPAR-α ligands, such as fibrates, decrease triglyceride levels and reduce the incidence of cardiovascular events and atherosclerosis [20]. The first evidence indicating a potential role for PPARs in the inflammatory response was the demonstration that leukotriene B4, a proinflammatory eicosanoid, binds to PPAR-α and induces the transcription of genes involved in ω- and β-oxidation [21]. It has been described that PPAR-α is expressed in human and mouse immune cells, including lymphocytes, macrophages, and dendritic cells, and numerous studies have implicated PPAR-α in the negative regulation of inflammatory responses. Different works using PPAR-α ligands have shown a reduction in the symptoms of inflammation and disease in several models, including models of allergic airway disease, arthritis, and inflammatory intestine disease [22].
Moreover, the role of PPAR-α in the heart has been shown with regards not only to the governing of myocardial energy metabolism and function (using both gain-of-function and loss-of-function murine models) but also to extrametabolic activities such as anti-inflammatory activities (see [23, 24], respectively, for a review). There are many works that have further implicated PPAR-α as an important regulator of inflammatory disease. For instance, it has been demonstrated that PPAR-α activators inhibit IL-1β-induced IL-6 secretion by human aortic smooth muscle cells in a dose-dependent manner [25]. PPAR-α activators also negatively regulate IL-1β-induced IL-6 production at the gene expression level by inhibiting NF-κB transcriptional activity [26]. In addition, other mechanisms, including alterations in cytokine-receptor and growth-factor receptor signaling, and the upregulation of the expression of a subunit of the inhibitor of NF-κB (IκB), have been reported (see [24] for a review).

3.2. PPAR-β/δ. PPAR-β, also known as PPAR-δ, is expressed ubiquitously and often at higher levels than PPAR-α and PPAR-γ, suggesting a fundamental role for it in many tissues. PPAR-δ was first identified in *Xenopus laevis* [27], and the mouse and human receptors were subsequently cloned on the basis of sequence similarity with PPAR-α [17]. PPAR-δ target genes in metabolic tissues are broadly involved in fatty acid metabolism, mitochondrial respiration, and thermogenesis. An in vitro study in endothelial cells has indicated that PPAR-β/δ ligands inhibit TNFα-induced upregulation of the expression of VCAM-1, MCP-1, and NF-κB translocation [28]. The role of PPAR-δ in the modulation of inflammation is poorly understood. It has been proposed that, in macrophages, PPAR-β/δ also controls inflammation by its association and disassociation with the transcriptional repressor BCL-6. It has also been described that the loss of hematopoietic PPAR-δ expression protects against atherosclerosis, being the proatherogenic effects of PPAR-δ due in part to the influence of PPAR-δ on the basal expression of inflammatory mediators in the arterial wall. It has also been found that PPAR-δ−/− bone-marrow-derived macrophages show reduced expression of CCL2, matrix metalloproteinase 9 (MMP9), and IL-1β and that the ligand binding to PPAR-δ releases BCL-6, resulting in the repression of inflammatory gene expression [29].

3.3. PPAR-γ. PPAR-γ is the most studied member of the PPAR family. Two distinct isoforms of PPAR-γ (PPAR-γ1 and PPAR-γ2), which are derived from the same gene but arise by differential transription start sites and alternative splicing, have been described [30]. This receptor has been cloned from a number of species, including mice, hamsters, frogs, pigs, monkeys, and humans [17, 27, 31]. PPAR-γ has a prominent expression in brown and white adipose tissue, the colon, differentiated myeloid cells and the placenta [32]. Brown and white adipocyte tissues are major sites for PPAR-γ expression. In 1995, Greene et al. identified two transcripts corresponding to a full-length mRNA and a short form devoid of functional domains [31]. More recent studies have demonstrated that the full-length PPAR-γ is indeed expressed in activated T and B cells and monocytes/macrophages [33–35].

The main physiological function of PPARs is the modulation of the expression of specific target genes [36]. PPAR-γ is critical for the differentiation of preadipocytes to adipocytes and also participates in glucose metabolism homeostasis [37, 38]. PPAR-γ can be activated by several physiological ligands, such as docosahexaenoic acid, linoleic acid, and some synthetic ones like antidiabetic glitazones, which are used as insulin sensitizers. Other ligands include oxidized LDL, azoyle PAF, and eicosanoids, such as 5,8,11,14-eicosatetraenoic acid and the prostanoids PGA1, PGA2, PGD2, and the dehydration products of the PG series of cyclopentanones, for example, 15-deoxy-Δ12,14-PGJ2 (15dPGJ2) [39]. In particular, the last one is recognized as an endogenous ligand for the intranuclear receptor PPAR-γ being responsible for many anti-inflammatory functions (see [40] for a review). However, previous studies have reported that PPARs inhibit inflammatory gene expression by several mechanisms, including direct interactions with AP1 and NF-κB [41–43], nuclear cytoplasmic redistribution of the p65.
subunit of NF-κB [44], modulation of p38 mitogen-activated protein kinase activity [45], competition for limiting pools of coactivators [46], and interactions with transcriptional corepressors [29] (see [47] for a review).

PPAR-γ has been reported to regulate inflammatory responses, both in vivo and in vitro, being involved in the regulation of macrophages and endothelial cells, both crucial to the inflammatory response. The presence of PPAR-γ in macrophages was first described in studies using human atheromas [48–51]. A role for PPAR-γ in T-lymphocyte atherosclerosis regulation has also been described [52]. Furthermore, PPAR-γ is involved in the differentiation and activation of monocytes and in the regulation of their inflammatory responses. Previous works have suggested that different stimuli increase monocytes/macrophages PPAR-γ expression [53, 54]. Anti-inflammatory effects of macrophage PPAR-γ activation have been demonstrated in a number of studies [55, 56].

The roles of 15dPGJ2 and PPAR-γ in the regulation of human autoimmune diseases or in animal models of autoimmunity have been studied by several groups.

15dPGJ2 and other PPAR-γ ligands inhibit inflammation in models of arthritis [57–59], ischemia-reperfusion injury [60], inflammatory bowel disease (IBD) [61–63], Alzheimer’s disease [64–66], and lupus nephritis [67, 68].

4. Can PPAR Promote or Prevent the Inflammatory Response after T. cruzi Infection?

Chagas disease is caused by infection with the protozoan kinetoplastid parasite Trypanosoma cruzi. Acute T. cruzi infection is accompanied by an intense inflammatory reaction in many tissues, being usually asymptomatic. When symptoms occur, they include prolonged fever, enlargement of the liver, spleen, and lymph nodes, subcutaneous edema (chagoma) or edema of the ocular mucous membranes (Romanián’s sign).

There are substantial evidences showing that the cardiac tissue is an important target of T. cruzi infection. Controlling the inflammatory reaction is critical for the control of the parasite proliferation in all the tissues, especially in the heart since it may progress to fibrosis and remodeling, resulting in a dilated cardiomyopathy accompanied by myocardial dysfunction [69]. In the context of inflammatory response, in a review of parasitic infections, Chan et al. (2010) argue that PPAR activation might favor the establishment of a chronic parasitic infection, making symbiotic survival between the host and parasite more probable [70]. In this sense, the adipose tissue has been identified as one of the main sites of inflammation during Chagas disease progression when cultured adipocytes are infected with the Tulahuen strain of T. cruzi, demonstrating an increase in the expression of proinflammatory mediators [71]. Fnu Nagajyothi et al. (2008) described an infection-associated decrease in adiponectin and PPAR-γ in infected adipocytes. They also showed that PPAR-γ is highly expressed in adipose tissue and that, together with the adipokine adiponectin, represses the inflammatory process although the mechanism by which adiponectin exerts an anti-inflammatory effect is unclear [71]. However, it is clear that a reduction in the level of adiponectin is associated with an increase in inflammation and that there is an inverse relationship between PPAR-γ and inflammation [71]. Another group of researchers has recently described in a mouse model of infection with the Colombian strain of T. cruzi (MHOM/CO/00/Colombian) that the treatment with 15dPGJ2 reduces the inflammatory infiltrate in the skeletal muscle at the site of infection and decreases the number of lymphocytes and neutrophils in the blood. These researchers also found that 15dPGJ2 also decreases the relative volume density of parasitic nests in cardiac muscle [72]. Many works have described that PPAR-α and PPAR-γ agonists play an important role in regulating inflammation in different models in vivo and in vitro. Recently, the role of rosiglitazone, a PPAR-γ synthetic agonist, in the modulation of the innate immune response has been demonstrated in an experimental cerebral malaria model (Reviewed in [70]). Also, it has been reported that rosiglitazone together with antischistosomal drugs improves the symptoms of liver fibrosis induced by Schistosoma japonicum in mice [70]. Besides, by linking metabolism and immunity, Gallardo-Soler et al. proposed that PPAR activity induces macrophage activation toward a more Th2 immune phenotype in a model of Leishmania major infection. These authors showed that PPAR-γ and PPAR-δ ligands promote intracellular amastigote growth in infected macrophages, and that this effect is dependent on both PPAR expression and arginase activity, suggesting that Arginase I is a key marker of the alternative program triggered by PPAR in macrophages [73].

Trypanosoma cruzi infection causes an intense inflammatory response in diverse tissues, including the heart. The inflammatory reaction is critical for the control of the parasites’ proliferation and evolution of Chagas disease. 15dPGJ2 can repress the inflammatory response in many experimental models. However, the precise role of PPAR-γ ligands in T. cruzi infection is poorly understood. Hovsepian et al. (2011) have recently reported the first evidence that 15dPGJ2 treatment increases the number of intracellular parasites and inhibits the expression and activity of different inflammatory enzymes such as inducible nitric oxide synthase (iNOS), matrix metalloproteinases 2 and 9 (MMP-2, MMP-9), as well as proinflammatory cytokine (TNF-α and IL-6) mRNA expression in neonatal mouse cardiomyocytes after T. cruzi infection [12] (Figure 2). They also observed that transfection of cardiomyocytes with small interfering RNA (siRNA) induces silencing of PPAR-γ and PPAR-δ in infection [74]. Hovsepian et al. (2011) demonstrated in T. cruzi-infected neonatal cardiac cells that PPAR-γ-independent pathways are involved, since
15dPGJ2 also exerts its effect through extracellular signal-regulated kinases-mitogen-activated protein kinase (Erk-MAPK) and NF-κB. The use of specific pharmacological inhibitors confirmed these findings [12] (Figure 2). Our group has recently found evidence about the role of 15dPGJ2 in the regulation of inflammation parameters in a mouse experimental model of *T. cruzi* infection, confirming all the results assayed in neonatal cardiomyocytes (data not shown).

**5. Perspectives**

To date, the accurate role of PPAR ligands in *T. cruzi* infection remains essentially unexplored. In this sense, some authors argue that the expression of PPAR-γ decreases after *T. cruzi* infection, while others argue that this expression increases. However, in general, most research groups highlight the role of PPARs in resolving inflammation and collaborating with tissue repair in some cases. Therefore, we hope that PPARs can potentially contribute to address a new pharmacological approach to improve the host health.

**Authors’ Contribution**

E. Hovsepian and F. Penas contributed equally in the paper.

**References**

[1] P. J. Hotez, D. H. Molyneux, A. Fenwick et al., “Control of neglected tropical diseases,” *New England Journal of Medicine*, vol. 357, no. 10, pp. 1018–1027, 2007.

[2] L. M. Deane, “Animal reservoirs of *Trypanosoma cruzi* in Brazil,” *Revista Brasileira de Malariologia e Doenças Tropicais*, vol. 16, pp. 27–48, 1964.

[3] A. Rassi Jr., A. Rassi, and J. A. Marin-Neto, “Chagas disease,” *The Lancet*, vol. 375, no. 9723, pp. 1388–1402, 2010.

[4] A. Prata, “Clinical and epidemiological aspects of Chagas disease,” *Lancet Infectious Diseases*, vol. 1, no. 2, pp. 92–100, 2001.

[5] J. C. P. Dias, “Natural history of Chagas’ disease,” *Arquivos Brasileiros de Cardiologia*, vol. 65, no. 4, pp. 359–366, 1995.

[6] R. L. Tarleton, R. Reithinger, J. A. Urbina, U. Kitron, and R. E. Gürtler, “The challenges of Chagas disease—Grim outlook or glimmer of hope?” *PLoS Medicine*, vol. 4, no. 12, article e332, 2007.

[7] A. Rassi Jr., A. Rassi, W. C. Little et al., “Development and validation of a risk score for predicting death in Chagas’ heart disease,” *New England Journal of Medicine*, vol. 355, no. 8, pp. 799–808, 2006.

[8] J. H. Maguire, “Chagas’ disease—can we stop the deaths?” *New England Journal of Medicine*, vol. 355, no. 8, pp. 760–761, 2006.

[9] J. A. Marin-Neto, E. Cunha-Neto, B. C. Maciel, and M. V. Simões, “Pathogenesis of chronic Chagas heart disease,” *Circulation*, vol. 115, no. 9, pp. 1109–1123, 2007.

[10] F. S. Machado, G. A. Martins, I. C. Aliberti, F. L. Mestriner, F. Q. Cunha, and J. S. Silva, “*Trypanosoma cruzi*-infected cardiomyocytes produce chemokines and cytokines that trigger potent nitric oxide-dependent trypanocidal activity,” *Circulation*, vol. 102, no. 24, pp. 3003–3008, 2000.

[11] F. S. Machado, J. T. Souto, M. A. Rossi et al., “Nitric oxide synthase-2 modulates chemokine production by *Trypanosoma*
cruzi-infected cardiac myocytes,” *Microbes and Infection*, vol. 10, no. 14-15, pp. 1558–1566, 2008.

[12] E. Hovsepian, G. A. Mirkin, F. Penas et al., “Modulation of inflammatory response and parasitism by 15-Deoxy-12,14 prostaglandin J(2) in *Trypanosoma cruzi*-infected cardomyocytes,” *International Journal for Parasitology*, vol. 41, pp. 553–562, 2011.

[13] N. R. N. Committee, “A unified nomenclature system for the nuclear receptor superfamily,” *Cell*, vol. 97, no. 2, pp. 161–163, 1999.

[14] D. J. Mangelsdorf and R. M. Evans, “The RXR heterodimers and orphan receptors,” *Cell*, vol. 83, no. 6, pp. 841–850, 1995.

[15] C. K. Glass and M. G. Rosenfeld, “The coregulator exchange in transcriptional functions of nuclear receptors,” *Genes and Development*, vol. 14, no. 2, pp. 121–141, 2000.

[16] S. A. Kliewer, K. Umesono, D. J. Noonan, R. A. Heyman, and I. Isseroff and S. Green, “Activation of a novel family of nuclear hormone receptors,” *Annual Review of Biochemistry*, vol. 68, no. 6662, pp. 79–82, 1998.

[17] B. Zingarelli, M. Sheehan, P. W. Hake, M. O’Connor, A. Mirko, S. W. Chung, B. Y. Kang, S. H. Kim et al., “Oxidized lipids: a high affinity ligand for peroxisome proliferator-activated receptor-α,” *Nature*, vol. 400, 2002.

[18] J. M. Lehmann, L. B. Moore, T. A. Smith-Oliver, W. O. Wilkison, T. M. Willson, and S. A. Kliewer, “Antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor γ (PPARγ),” *Journal of Biological Chemistry*, vol. 270, no. 22, pp. 12953–12956, 1995.

[19] J. A. Madrazo and D. P. Kelly, “The PPAR trio: regulators of myocardial energy metabolism in health and disease,” *Journal of Molecular and Cellular Cardiology*, vol. 44, no. 6, pp. 968–975, 2008.

[20] P. Lockyer, J. C. Schisler, C. Patterson, and M. S. Willis, “Mini-review: won’t get fooled again: the nonmetabolic roles of peroxisome proliferator-activated receptors (PPARs) in the heart,” *Molecular Endocrinology*, vol. 24, no. 6, pp. 1111–1119, 2010.

[21] B. Staels, W. Koenig, A. Habib et al., “Activation of human aortic smooth-muscle cells is inhibited by PPARα but not by PPARγ activators,” *Nature*, vol. 393, no. 6687, pp. 790–793, 1998.

[22] P. Delerive, K. de Bosscher, W. V. Berghe, J.-C. Fruchart, G. Haegeman, and B. Staels, “DNA binding-independent induction of 1kBa gene transcription by PPARα,” *Molecular Endocrinology*, vol. 16, no. 5, pp. 1029–1039, 2002.

[23] C. Dreyer, G. Krey, H. Keller, F. Givel, G. Helftenbein, and W. Wahli, “Control of the peroxisomal β-oxidation pathway by a novel family of nuclear hormone receptors,” *Cell*, vol. 68, no. 5, pp. 879–887, 1992.

[24] Y. Rival, N. Benêteau, T. Taillandier et al., “PPARα and PPARγ activators inhibit cytokine-induced nuclear translocation of NF-κB and expression of VCAM-1 in EAHy926 endothelial cells,” *European Journal of Pharmacology*, vol. 435, no. 2-3, pp. 143–151, 2002.

[25] C. H. Lee, A. Chawla, N. Urbiztondo, D. Liao, W. A. Boisvert, and R. M. Evans, “Transcriptional repression of atherogenic inflammation: modulation by PPARγ,” *Science*, vol. 302, no. 5644, pp. 453–457, 2003.

[26] L. Fajas, H. Auboeuf, E. Raspé et al., “The organization, promoter analysis, and expression of the human PPARγ gene,” *Journal of Biological Chemistry*, vol. 272, no. 30, pp. 18779–18789, 1997.

[27] M. E. Greene, B. Blumberg, O. W. McBride et al., “Isolation of the human peroxisome proliferator activated receptor gamma cDNA: expression in hematopoietic cells and chromosomal mapping,” *Gene Expression*, vol. 4, no. 4-5, pp. 281–299, 1995.

[28] T. M. Willson, M. H. Lambert, and S. A. Kliewer, “Peroxisome proliferator-activated receptor γ and metabolic disease,” *Annual Review of Biochemistry*, vol. 70, pp. 341–367, 2001.

[29] M. Ricote, A. C. Li, T. M. Willson, C. J. Kelly, and C. K. Glass, “The peroxisome proliferator-activated receptor-γ is a negative regulator of macrophage activation,” *Nature*, vol. 391, no. 6662, pp. 79–82, 1998.

[30] S. G. Harris and R. P. Phipps, “The nuclear receptor PPAR γ is expressed by mouse T lymphocytes and PPAR γ agonists induce apoptosis,” *European Journal of Immunology*, vol. 31, no. 4, pp. 1098–1105, 2001.

[31] R. B. Clark, “The role of PPARs in inflammation and immunity,” *Journal of Leukocyte Biology*, vol. 71, no. 3, pp. 388–400, 2002.

[32] P. Tontonoz, E. Hu, and B. M. Spiegelman, “Stimulation of adipogenesis in fibroblasts by PPARγ2, a lipid-activated transcription factor,” *Cell*, vol. 79, no. 7, pp. 1147–1156, 1994.

[33] Y. Barak, M. C. Nelson, E. S. Ong et al., “PPARγ is required for placentation, cardiac, and adipose tissue development,” *Molecular Cell*, vol. 4, no. 4, pp. 585–595, 1999.

[34] J. A. Madrazo and D. P. Kelly, “The PPAR trio: regulators of myocardial energy metabolism in health and disease,” *Annual Review of Cell and Developmental Biology*, vol. 11, pp. 879–887, 1995.
ciglitazone, reduce systemic inflammation in polymicrobial sepsis by modulation of signal transduction pathways,” *Journal of Immunology*, vol. 171, no. 12, pp. 6827–6837, 2003.

[44] D. Kelly, J. I. Campbell, T. P. King et al., “Commensal anaerobic gut bacteria a tenuate inflammation by regulating nuclear-cytoplasmic shuttling of PPAR-γ and RelA,” *Nature Immunology*, vol. 5, pp. 104–112, 2004.

[45] T. Syrovets, A. Schule, M. Jendrach, B. Buchele, and T. Simmet, “Ciglitazone inhibits plasminduced proinflammatory monocyte activation via modulation of p38 MAP kinase activity,” *Thrombosis and Haemostasis*, vol. 88, pp. 274–281, 2002.

[46] M. Li, G. Pascual, and C. K. Glass, “Peroxisome proliferator-activated receptor γ-dependent repression of the inducible nitric oxide synthase gene,” *Molecular and Cellular Biology*, vol. 20, no. 13, pp. 4699–4707, 2000.

[47] S. J. Bensinger and P. Tontonoz, “Integration of metabolism and inflammation by lipid-activated nuclear receptors,” *Nature*, vol. 454, no. 7203, pp. 470–477, 2008.

[48] N. Marx, G. Sukhova, C. Murphy, P. Libby, and J. Plutzky, “Macrophages in human atheroma contain PPARγ; differentiation-dependent peroxisomal proliferator-activated receptor γ (PPARγ) expression and reduction of MMP-9 activity through PPARγ activation in mononuclear phagocytes in vitro,” *American Journal of Pathology*, vol. 153, no. 1, pp. 17–23, 1998.

[49] N. Marx, “Peroxisome proliferator-activated receptor gamma and atherosclerosis,” *Current Hypertension Reports*, vol. 4, no. 1, pp. 71–77, 2002.

[50] G. Chinetti, J. C. Fruchart, and B. Staels, “Peroxisome proliferator-activated receptors (PPARs): nuclear receptors at the crossroads between lipid metabolism and inflammation,” *Inflammation Research*, vol. 49, no. 10, pp. 497–505, 2000.

[51] C. Duval, G. Chinetti, F. Trottein, J. C. Fruchart, and B. Staels, “The role of PPARs in atherosclerosis,” *Trends in Molecular Medicine*, vol. 8, no. 9, pp. 422–430, 2002.

[52] R. B. Clark, “The role of PPARs in inflammation and immunity,” *Journal of Leukocyte Biology*, vol. 71, no. 3, pp. 388–400, 2002.

[53] M. Ricote, J. Huang, L. Fajas et al., “Expression of the peroxisome proliferator-activated receptor γ (PPARγ) in human atherosclerosis and regulation in macrophages by colony stimulating factors and oxidized low density lipoprotein,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 95, no. 13, pp. 7614–7619, 1998.

[54] G. Chinetti, S. Griglio, M. Antonucci et al., “Activation of proliferator-activated receptors a and y induces apoptosis of human monocyte-derived macrophages,” *Journal of Biological Chemistry*, vol. 273, no. 40, pp. 25573–25580, 1998.

[55] M. Ricote, A. C. Li, T. M. Willson, C. J. Kelly, and C. K. Glass, “The PPAR-γ-responsive receptor-activated receptor-γ is a negative regulator of macrophage activation,” *Nature*, vol. 391, no. 6662, pp. 79–82, 1998.

[56] A. F. Valledor and M. Ricote, “Nuclear receptor signaling in macrophages,” *Biochemical Pharmacology*, vol. 67, no. 2, pp. 201–212, 2004.

[57] Y. Kawahito, M. Kondo, Y. Tsubouchi et al., “15-deoxy-Δ12,14-PGJ2 induces synoviocyte apoptosis and suppresses adjuvant-induced arthritis in rats,” *Journal of Clinical Investigation*, vol. 106, no. 2, pp. 189–197, 2000.

[58] H. Fahmi, J. A. di Battista, J. P. Pelletier, F. Mineau, P. Ranger, and J. Martel-Pelletier, “Peroxisome proliferator-activated receptor γ activators inhibit interleukin-1β-induced nitric oxide and matrix metalloproteinase 13 production in human chondrocytes,” *Arthritis and Rheumatism*, vol. 44, no. 3, pp. 595–607, 2001.

[59] K. Bordji, J.-P. Grillasca, J.-N. Gouze et al., “Evidence for the presence of peroxisome proliferator-activated receptor (PPAR) α and γ and retinoid Z receptor in cartilage. PPARγ activation modulates the effects of interleukin-1β on rat chondrocytes,” *Journal of Biological Chemistry*, vol. 275, no. 16, pp. 12243–12250, 2000.

[60] A. Nakajima, K. Wada, H. Miki et al., “Endogenous PPARγ mediates anti-inflammatory activity in murine ischemia-reperfusion injury,” *Gastroenterology*, vol. 120, no. 2, pp. 460–469, 2001.

[61] C. G. Su and J. D. Lewis, “Antineoplastic and anti-inflammatory effects of PPAR ligands in colitis,” *Gastroenterology*, vol. 121, no. 4, pp. 1019–1021, 2001.

[62] C. G. Su, X. Wen, S. T. Bailey et al., “A novel therapy for colitis utilizing PPAR-γ ligands to inhibit the epithelial inflammatory response,” *Journal of Clinical Investigation*, vol. 104, no. 4, pp. 383–389, 1999.

[63] K. Wada, A. Nakajima, and R. S. Blumberg, “PPARγ and inflammatory bowel disease: a new therapeutic target for ulcerative colitis and Crohn’s disease,” *Trends in Molecular Medicine*, vol. 7, no. 8, pp. 329–331, 2001.

[64] C. K. Combs, D. E. Johnson, J. C. Karlo, S. B. Cannady, and G. E. Landreth, “Inflammatory mechanisms in Alzheimer’s disease: inhibition of β-amyloid-stimulated proinflammatory responses and neurotoxicity by PPARγ agonists,” *Journal of Neuroscience*, vol. 20, no. 2, pp. 558–567, 2000.

[65] M. T. Heneka, T. Klockgether, and D. L. Feinstein, “Peroxisome proliferator-activated receptor-γ ligands reduce neuronal inducible nitric oxide synthase expression and cell death in vivo,” *Journal of Neuroscience*, vol. 20, no. 18, pp. 6862–6867, 2000.

[66] G. E. Landreth and M. T. Heneka, “Anti-inflammatory actions of peroxisome proliferator-activated receptor gamma agonists in Alzheimer’s disease,” *Neurobiology of Aging*, vol. 22, no. 6, pp. 937–944, 2001.

[67] C. M. Reilly, J. C. Oates, J. A. Cook, J. D. Morrow, P. V. Halushka, and G. S. Gilkeson, “Inhibition of mesangial cell nitric oxide in MRL/lpr mice by prostaglandin J2 and proliferator activation receptor-γ agonists,” *Journal of Immunology*, vol. 164, no. 3, pp. 1498–1504, 2000.

[68] C. M. Reilly, J. C. Oates, J. Sudian, M. B. Crosby, P. V. Halushka, and G. S. Gilkeson, “Prostaglandin J2 inhibition of mesangial cell iNOS expression,” *Clinical Immunology*, vol. 98, no. 3, pp. 337–345, 2001.

[69] M. L. Higuchi, L. A. Benvenuti, M. M. Reis, and M. Metzger, “Pathophysiology of the heart in Chagas’ disease: current status and new developments,” *Cardiovascular Research*, vol. 60, no. 1, pp. 96–107, 2003.

[70] M. M. Chan, K. W. Evans, A. R. Moore, and D. Fong, “Peroxisome proliferator-activated receptor (PPAR): balance for survival in parasitic infections,” *Journal of Biomedicine & Biotechnology*, vol. 2010, Article ID 828951, 2010.

[71] F. Nagajyothi, M. S. Desruisseaux, N. Thiruvur et al., “Trypanosoma cruzi Infection of cultured adipocytes results in an inflammatory phenotype,” *Obesity*, vol. 16, no. 9, pp. 1992–1997, 2008.

[72] W. F. Rodrigues, C. B. Miguel, J. E. Chica, and M. H. Napimoga, “15d-PGJ2 modulates acute immune responses to *Trypanosoma cruzi* infection,” *Memorias do Instituto Oswaldo Cruz*, vol. 105, no. 2, pp. 137–143, 2010.

[73] A. Gallardo-Soler, C. Gómez-Nieto, M. L. Campo et al., “Ariginase I induction by modified lipoproteins in macrophages:
a peroxisome proliferator-activated receptor-γ/δ-mediated effect that links lipid metabolism and immunity, “Molecular Endocrinology, vol. 22, no. 6, pp. 1394–1402, 2008.

[74] E. Hovsepian, F. Penas, and N. B. Goren, “15-deoxy-Δ12,14 prostaglandin GJ2 but not rosiglitazone regulates metalloproteinase 9, NOS-2, and cyclooxygenase 2 expression and functions by peroxisome proliferatory activated receptor γ-dependent and-independent mechanisms in cardiac cells,” Shock, vol. 34, no. 1, pp. 60–67, 2010.