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Review Article

Physiology and Pathophysiology of PPARs in the Eye

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Abstract. Peroxisome proliferator-activated receptor (PPARs) are ligand-activated transcription factors that exert significant roles in the control of multiple physiological processes. The last decade has shown an increasing interest in the role played by the agonists of PPARs in anti-inflammatory, anti-angiogenic, anti-fibrotic effects and in modulating oxidative stress response in different organs. Since the pathologic mechanisms of the majority of the blinding diseases, such as diabetic retinopathy (DR), age-related macular degeneration (AMD), glaucoma and optic neuropathy (ON), often involve neo-angiogenesis, inflammation and oxidative stress-mediated cell death, evidences are accumulating on the potential benefits of PPAR modulation to prevent or ameliorate eye pathologies. In this review, we focused on the description of what is known about the role of PPARs in the ocular pathophysiological processes and on PPARs agonists as innovative adjuvants in the treatment of ocular diseases.

Keywords: PPARs; eye, ocular pathology; PPARs agonist; PPARs antagonist

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1. Introduction

Peroxisome proliferator-activated receptor (PPARs), a constituent of the nuclear receptor superfamily, is a ligand-activated transcription factor that plays a key role in the control of gene expression linked to various physiological processes [1]. PPAR has been first identified by homology cloning in Xenopus [2] and mice [3] and then in mammals [4]. It is most broadly expressed in adipose tissue, but also in immune/inflammatory cells (e.g., macrophages, monocytes), skeletal muscle, mucosa of the colon and cecum, kidney, heart, liver, the eyeball, and lung, [5–8]. PPARs, like the other nuclear receptors, is included in distinct functional domains, among which an N-terminal transactivation domain (AF1), a highly conserved DNA-binding domain (DBD), and a C-terminal ligand-binding domain (LBD) containing a ligand-dependent trans-activation function (AF2) [9]. PPARs can regulate transcription by numerous mechanisms, including ligand-independent repression, ligand-dependent trans-repression, and ligand-dependent transactivation. PPARs is triggered by heterodimerization with the retinoid X receptor (RXR) into biologically active transcription factor and afterwards binds to peroxisome proliferator response elements (PPREs), thus acting as a transcriptional regulator [10, 11]. Moreover, PPARs is capable of modulating gene expression independently of binding to PPREs. PPARs owns a large T-shaped ligand-binding pocket that allows interaction with a structurally diverse library of ligands [12]. Endogenous ligands for PPARs include, nitrated fatty acids, unsaturated and oxidized fatty acids, prostaglandins and eicosanoids [13]. Thiazolidinediones (TZDs)

among which pioglitazone, troglitazone, and rosiglitazone are synthetic PPARγ ligands with the capability to increase insulin sensitivity in humans and animals [14, 15]; some of the TZDs are already in clinical application as insulin sensitizers in type 2 diabetic patients [16]. Due to the increasing number of scientific reports, PPARs ligands are in rapidly growing for their leading role in regulating metabolic processes.

Three PPARs: PPARα, PPARβ/δ, and PPARγ, have been recognized [2]. PPARα is largely expressed in heart, liver, stomach mucosa, kidney, and brown adipose tissue; PPARγ has been found principally in adipose tissue; PPARβ/δ is the most ubiquitously expressed [3, 4], however its roles in physiological and pathophysiological processes are still unclear, especially, in human tissue. The recent development of PPARβ/δ knockout and transgenic mice has started to implicate roles for PPARβ/δ in metabolism, adipose tissue formation, brain development, wound healing, atherosclerosis, placental function, skeletal muscle function and colorectal carcinogenesis [5–7].

In this review we discuss the knowledge regarding the role of PPARs in ocular pathophysiological processes and PPARs agonists as innovative adjuvants in the treatment of ocular diseases.

The majority of the studies have focused on PPARγ, in the light of its central role in the inflammation; while only few reports about PPARα and PPARβ/δ are present.

2. PPARs Expression in the Eye

All different isoforms of PPARs are constitutively expressed in the whole retina [17] but most of reports are referred to the retinal pigment epithelia (RPE). As it has recently reported from Ciudin and collaborators, PPARs are expressed in cultures of ARPE19 cells (a human immortalized line of RPE cells) and primary RPE cells [18–20]. ARPE19 cells as well as RPE do not express PPARγ2 and moderately express PPARγ1 and PPARβ. Primary RPE cells express low levels of PPARα, whereas the ARPE-19 cells presented moderate levels. Interestingly, it has been evaluated the PPARs expression in the freshly isolated RPE, and the results were slightly different from the cell cultures: a high representation of PPARα and PPAR β and a deficiency of PPARγ1 and PPARγ2 expression [18–20].

In an interesting paper, it has been demonstrated that that PPAR α, β and γ were diffusely expressed in normal neuroretina and RPE of humans as well as mice [17]. PPARγ is heterogeneously expressed in the mammalian eye [21]. The eyeball, specifically the retina, is the extended part of the brain, therefore, eye development is highly correlated with the CNS. It has been provided that PPARγ is expressed in the retina, and is involved in many physiological and pathological processes, such as, age-related macular degeneration [22, 23], retinal neuroprotection [24, 25], and diabetic retinopathy [22, 29–31].

PPARγ is highly represented in the retinal pigmented epithelium, in the iris choroidal endothelial cells, in choriocapillaris, in corneal endothelium and epithelium, and to a smaller extent in the intraocular muscles, retinal photoreceptor inner segments and outer plexiform layer and photoreceptor outer segments. It has been suggested in recent studies that PPARγ exert a pivotal role in oxidative stress response modulating the activation of several antioxidants involved in oxidative stress and influencing apoptotic or necrotic cell death [26–28].

Regarding the immune system, it has been indicated that PPARγ has a key role in regulating inflammatory gene expression [29].

Since the pathologic mechanisms of most of blinding diseases, such as age-related macular degeneration (AMD), diabetic retinopathy (DR), and optic neuropathy, often involve neoangiogenesis and inflammation- and oxidative stress-mediated cell death, numerous evidences are accumulating on the potential benefits of PPARγ to prevent or ameliorate eye diseases.

Ligand-dependent activation of PPARγ evokes potent inhibition of neovascularization and corneal angiogenesis as it has been described by Sarayba and collaborators [30]; more specifically, they suggest that Pioglitazone is a promising drug for treating ocular neovascularization, since it is effective in decreasing the density of angiogenesis in a VEGF-induced neovascular rat cornea model. The conspicuous expression of PPARγ in selected tissues of the retina provides the rationale for pharmacotherapeutic targeting of PPARγ for treating proliferative retinopathies and ocular inflammation [30, 31].

PPARβ/δ is abundantly expressed in the murine ocular tissue. It is expressed in the eye ciliary body epithelial cells, corneal epithelial cells, retina inner nuclear layer, retinal ganglion cell layer, corneal fibroblast, and corneal endothelium [32].

The effects of PPAR β in the eye are not very well known. Numerous studies have associated PPARβ activation with proangiogenic and proinflammatory effects. PPARβ induces VEGF and angiogenesis in different cell types. This suggests that PPARβ antagonist could be useful to treat models of eye disease involving neovascularization. However, the action of PPARβ seems consistent with that of the other PPARs since it also exerts anti-inflammatory activity, suggesting that its activities in ocular angiogenesis may be more complex [33].

PPARα is present in the retina and in the cornea where it plays a protective anti-oxidant and wound healing effect [34]. Lipid use in retinal neurons is newly identified, the mediators of retinal fatty acid oxidation (FAO) are currently unknown. Recently, Pearsall and collaborators demonstrated a leading role for peroxisome proliferator activated receptor-alpha (PPARα) in retinal FAO, and furthermore, they indicated that FAO is crucial for the survival and maintenance of retinal neurons in physiological conditions [35].

3. PPAR and Ocular Disease

3.1. Diabetic retinopathy

Diabetic retinopathy (DR) represents the leading cause of blindness, including working age individuals in developing countries, which is one of the most usual microvascular complications of diabetes. TZDs, synthetic PPARγ agonists, besides regulating lipid metabolism and increasing insulin sensitivity [22], also play anti-atherogenic, anti-inflammatory, neuroprotective and antioxidative effects [22, 29–31]. Since these beneficial effects, they may exert therapeutic potential in diabetic microvascular complications such as DR.

In view of the role of inflammation in the pathogenesis of DR, it has been proposed that PPARγ ligands have therapeutic effects also as modulators of inflammation, other than providing glycemic control [33]. In diabetic patients, PPARγ agonists decrease several markers of inflammation, among which IL-6, serum levels of C-reactive protein, monocyte chemoattractant

protein-1 (MCP-1), soluble CD40 ligand, matrix metalloproteinase-9 and plasminogen activator inhibitor-1, [29, 36]. Moreover, they have been demonstrated to suppress activated NFκB and decrease ROS generation in blood mononuclear cells [28, 29].

Alteration of the inflammatory process has also been analyzed in DR animal models. In streptozotocin-induced DR, rosiglitazone has been demonstrated to inhibit both retinal leukostasis and retinal leakage [37]. The effect was not linked to down-regulation of proinflammatory cytokines, even though a reduction of the adhesion molecule ICAM was observed. Nitric Oxide (NO) of endothelial origin regulates ocular blood flow. In the endothelial dysfunction, which characterizes the initial stages of DR, a reduction in the bioavailability of NO may participate to impairment of ocular hemodynamics [38].

To clarify whether endogenous PPARγ and its ligand, rosiglitazone, affect retinal leukostasis and the consequent vascular leakage, Muranaka and collaborators [37] used experimental diabetic *in vivo* models, more precisely, streptozotocin-induced diabetic C57BL/6 mice deficient for PPARγ expression (heterozygous genotype, PPARγ+/−) and Brown Norway rats. Retinal leukostasis and leakage, quantified by concanavalin A (Con A) lectin perfusion labeling combined with a fluorophotometric dextran leakage assay, were investigated at 120 days in diabetic PPARgamma+/- and wild-type mice and at 21 days in diabetic rats receiving rosiglitazone or the vehicle. Retinal leukostasis and leakage were greater in the diabetic PPARγ+/− mice, with respect to diabetic wild-type animal. Retinal leukostasis and leakage in diabetic rats were suppressed by rosiglitazone treatment. It has been also demonstrated that the upregulated ICAM-1 expression in the diabetic rat retina was reduced by rosiglitazone treatment. These results suggest that an endogenous pathway, involving PPARγ, provides protection against retinal leukostasis and retinal leakage in diabetes. In addition, treatment with PPARγ specific ligands, such as rosiglitazone, can diminish the progression of DR, since it has been demonstrated to inhibit retinal leukostasis and retinal leakage in diabetic rats [37].

Other studies demonstrated that administration of troglitazone [39] and pioglitazone [40] significantly increased plasma VEGF expression in diabetic patients, which consequently determines higher risk of diabetic macular edema (DME) and the progression of DR. The association between DME and TZDs is still debated [22, 41]. Various authors reported that fluid retention in the macula or subclinical DME under TZDs treatment was never observed [42, 43]. Additional experimental and clinical studies are, however, necessary.

Apart from these synthetic PPAR agonists, traditional and herbal natural medicines, among which Astragalus membranaceus, Swietenia Mahagoni [44], Pueraria thomsonii [44], Danshao-huaxian formula [45], Korean red ginseng [46], and Turmeric [47], have exhibited the potential effect in modulating DR *via* PPARs activation. Huang's group reviewed some studies on herbal or traditional medicine related to PPARs activation and on the probable mechanisms applied in the control of DR [8]. They established that plant-derived PPARs activators can represent a co-adjuvant or alternative therapy to delay or counteract the evolution of DR.

The role and the effect of PPARβ/δ in the eye and its effects in the diabetic eye are not well known and well-studied. Most of the studies have related PPARβ/δ activation with pro-inflammatory and pro-angiogenic effects; in fact, it has been demonstrated that the PPARβ/δ agonist, GW501516, increased VEGF expression and stimulates angiogenesis [48]. Taken together, PPARβ/δ is likely to play a role in DR, both in the components of inflammation and angiogenesis, although its effect remains to be clarified.

Regarding PPARα, since 1969 there are clinical evidences of a beneficial effect of PPARα activation on diabetic retinopathy; in fact, Harrold and collaborators, demonstrated amelioration in retinal exudate after 1 year of treatment with clofibrate, without significant influences on other retinal injuries [49]. This was confirmed by Dorne in 1977, who proposed clofibrate as therapy for exudative diabetic retinopathy [50].

While, in a more recent work, it has been determined the expression of PPARα in the retina and it has been demonstrated down-regulation of PPARα in the retina of diabetes models. Furthermore, it has been also induced diabetes in PPARα-knockout mice that displayed more severe retinopathy than diabetic wild- type mice, in fact, they showed severe diabetes-induced retinal vascular leakage and retinal inflammation, while, PPARα overexpression in the retina of diabetic rats significantly alleviated DR. This study reveals that PPARα has an anti-inflammatory function in the retina and it also suggest that diabetes-induced down-regulation of PPARα plays an important role in DR and represents a novel therapeutic strategy of clinical relevance [51]

Moreover, in another report, it has been demonstrated that PPARα agonism can exert pro-inflammatory and pro-angiogenic effects in ocular cells; in particular, the effect of WY-14 643, a selective PPARα agonist, on inflammatory cytokine released in human ocular cells was studied [34] and it was reported that WY-14643 significantly up-regulates vascular endothelial growth factor (VEGF) expression in this experimental model [34]. It has been shown that PPARα plays a neuroprotective role in several diseases, and it also involved in vascular homeostasis. Recently, two perspective clinical studies identified that the PPARα agonist fenofibrate had a robust therapeutic effect in diabetic retinopathy, although the molecular mechanism(s) of action remain poorly understood [52].

The recent evidence that PPARα activation has a positive effect in DR derives from two seminal clinical trials: the FIELD [53] and the ACCORD-Eye [52], which reported that DR progression was considerably decreased by fenofibrate (a PPARα as a hypolipedemic agent).

The FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) Study illustrates the possibility of DR prevention by therapy with fenofibrate. [53].

In this ophthalmological sub-study, retinopathy status and severity were assessed from two-field 45˚ color fundus photographs of the macula (stereoscopic) and a disc/nasal field taken at baseline, 2 years and 5 years, and graded with Early Treatment Diabetic Retinopathy Study (ETDRS) criteria. A considerable and evident reduction (~70%) in the risk of laser therapy for retinopathy was again confirmed for fenofibrate versus placebo. Nevertheless, only 28 patients needed laser treatment (23 in the placebo group and 5 in the fenofibrate group). Furthermore, DR progression was significantly weakened with fenofibrate in those patients with pre-existing DR at baseline (from 14.6% to 3.1%), but not in those without DR at baseline. Nonetheless, the number of events was slight (14 in the placebo group and 3 in the fenofibrate group).

The ACCORD trial comprised a lipid arm, in which patients were randomly indicated for treatment with placebo or fenofibrate in combination with open-label simvastatin [52]. Patients appropriate for this arm were also registered for the glycemia evaluation but additional recruitment criteria connecting to lipids (LDL cholesterol 1.55–4.65 mmol/L, HDL cholesterol <1.29 mmol/L [<1.42 mmol/L for women], and triglycerides <8.5 mmol/L [<4.5 mmol/L if receiving lipid-modifying therapy]). Retinopathy outcomes in ACCORD were assessed in a 4-year eye sub-study [52]. Randomization to fenofibrate relative to placebo (on background treatment with simvastatin) was related to an important decrease (from 10.2% to 6.5%,) in DR progression (3

or more steps on the EDTRS), with greater effect in patients with evidence of DR at baseline (absolute RR 6.9% versus 0.2% in those without DR at baseline). It should be highlighted that the decrease obtained with fenofibrate in combination with simvastatin (−40%) was even greater than that obtained in the arm of intensive glycemic control (−33%).

The comparisons between the effects of fenofibrate in the eye among the ACCORD-EYE and the FIELD studies are noticeable. In both trials, randomization to fenofibrate plus statin in a substantial proportion of patients by study end in FIELD, and entirely with a statin in ACCORD-EYE lead to clinically and statistically substantial decreases in the risk of a range of clinical endpoints associated with retinopathy [52, 53]. Summarizing, these trials displayed that fenofibrate therapy supports a relative decrease in DR progress of 30–40% over 4 to 6 years, with a significant advantage in patients with pre-existing DR. The FIELD and the ACCORD studies reported a reduced need for laser therapy and a slower progression of retinopathy with fenofibrate treatment. [52, 53].

3.2. Dry eye

Recently, Chen *et al.* [54] described that the PPARγ expression in the conjunctiva of dry eye mice was down-regulated, accompanied by augmented contents of inflammatory cytokines, TNF- and IL-1. They also reported that pioglitazone could activate PPARγ to contain the inflammatory progression, elevate the tear film stability, intensify the tear fluid production, and diminish the injury to the ocular surface, showing a therapeutic effect on dry eye. In cultured lacrimal gland acinar cells, pioglitazone may inhibit NO production, which excessive synthesis can be detrimental for the normal function of the lacrimal gland, thus proposing that the use of PPARγ agonist may offer an effective therapeutic intervention for the prevention of dry eye caused by reduction or lack of lacrimal gland secretion [55].

3.3. Age-related macular degeneration

Age-related macular degeneration (AMD) is the principal cause of vision loss in older people in the Western world. It is characterized by degeneration of the macula, the main area of the retina, with the highest concentration of cone photoreceptors, responsible for visual perception and colour vision. In AMD two stages has been identified: the early stage, is characterized by the formation of large drusen and pigmentary abnormalities [56]; the late stage is divided into two groups: nonexudative (“dry” form) and an exudative/neovascular (“wet” form). The nonexudative form is marked by atrophic changes in the macula and clinically, has a slower deterioration and better preservation of visual acuity than exudative AMD [56]. Exudative AMD involves choroidal neovascularization, which is the formation of new abnormal blood vessels in the choriocapillaries through Bruch’s membrane. These vessels tend to induce leakage and bleeding into the macula, and finally lead to irreversible injury to photoreceptors if left untreated [56]. Therefore, the exudative form accounts for most cases of significant visual loss from AMD [57]. Several groups of research indicate that PPARs may be implicated in numerous chemical pathways linked with AMD. PPARγ is constitutively expressed in retinal pigmented epithelial (RPE) cells of mice and humans and in normal neuroretina. Nevertheless, the expression of PPARγ is significantly greater than normal in both $Ccl2^{-/-}$/$Cx3cr1^{-/-}$ mice

(an AMD model) and AMD patients [17]. The exudative form of AMD, marked by choroidal neovascularization (CNV), is supposed to be responsible for most of the events of severe visual loss in this disease. Murata et al. [58] have proved that PPARγ ligands rosiglitazone or troglitazone, considerably reduced VEGF-induced migration and proliferation of RPE and choroidal endothelial cells and choroidal angiogenesis *in vitro*. In the eyes of monkeys and rat, in which CNV was provoked by laser photocoagulation, intravitreal injection of troglitazone intensely inhibited the percentage of lesions but also leakage per lesion. Increased intake of omega-3 long-chain polyunsaturated fatty acids (-3 LCPUFAs), endogenous agonists of PPARs [59, 60], is related with an attenuation of pathologic retinal and choroidal angiogenesis [61]. More recently, San Giovanni and colleagues discovered that DNA sequence variation in PPARs coactivator 1α, a gene encoding a coactivator of the -3 LCPUFAs-sensing PPAR-retinoid X receptor (RXR) transcription complex, can influence neovascularization in AMD [62]. The results propose that multiple constituent ligands and transcriptional coactivators of the PPAR-RXR system can alter pathogenic processes in CNV. There is a suggestion that dysfunction of RPE around the macula area may be responsible for the development of AMD [57, 63]. One of the most principal functions of RPE is phagocytic uptake and degradation of photoreceptor outer segments [19]. A report indicated that specific phagocytosis of photoreceptor outer segments by RPE cells selectively activates expression of PPARγ, proposing that PPARγ can exert a significant role in the photoreceptor renewal process [63]. Oxidative stress is a main risk factor causing RPE cell degeneration. Several studies have demonstrated that RPE might be the key target for oxidative stress and PPARs are involved in the oxidative stress signaling. In ARPE-19 cells and/or cultured human primary RPE cells, it has been indicated that troglitazone and 15d-PGJ2 protect cells from oxidative stress induced by butylhydroperoxide or HO [21, 63]. Other PPARs agonists, such as pioglitazone [40], azelaoyl PAF [63], ciglitazone [63], rosiglitazone [19, 40], AGN195037 [19], WY14643 [63] and LY171883 [63], however, were not effective. To understand whether the cytoprotective effects of troglitazone and 15d-PGJ2 are mediated by PPAR, PPARγ expression was knocked-down through RNA interference. In PPARγ-deficient cells, the positive effect of troglitazones was considerably inhibited [39], whereas 15d-PGJ2 protective activity was not altered [19]. These data showed that the cytoprotective effect of troglitazone is PPAR-mediated, while the 15d-PGJ2-effect is PPAR-independent, and that PPARs agonists may exert various effects on RPE survival upon oxidative stress [63].

Other interesting studies [64, 65] demonstrated for the first time a role of PPARβ/δ in regulating different aspects of extracellular matrix turnover, angiogenesis, inflammation, and lipid processing in the eye. PPARβ/δ affects the RPE and choroidal endothelium differentially, selectively impacting the development of several fundamental AMD phenotypes. In this study, it has been shown that PPARβ/δ activity is functionally important in RPE and choroidal endothelial cell models systems. PPARβ/δ knock-down expression led to an upregulation of extracellular matrix gene expression in primary RPE cells but to a downregulation in choroidal endothelial cells. Moreover, it has been observed a PPARβ/δ-dependent downregulation of the expression of critical factors for angiogenesis (including VEGF, PDGFR and TGF) in both cell populations, supporting the hypothesis that PPARβ/δ regulates crucial pathways in the development of neovascular lesions. Consistent with the *in vitro* studies, a significant decrease in area and volume of laser induced neovascular lesions was observed in both aged Pparβ/$\delta^{-/-}$ and in Pparβ/$\delta^{+/+}$ mice following pharmacological antagonism of the receptor. In contrast to these findings, morphological characterization of the ocular phenotype of aged Pparβ/$\delta^{-/-}$ mice revealed

the intensification and the development of several features of the early dry AMD phenotype, including continuous sub-RPE deposits, increased RPE autofluorescence, Bruch's membrane thickening, RPE pigmentary changes and disorganized basal infoldings. These *in vivo* results are supported by *in vitro* data, demonstrating increased dysregulation of extracellular matrix molecules following PPARβ/δ knockdown in human RPE cells. These findings illustrate, for the first time, cell-specific effects of PPARβ/δ in two populations of AMD cells and correlate with the concept of selective modulation of PPARs and other nuclear receptors [65].

Feldman and Co-Authors [65] examined the effect of ligand activation and pharmacological antagonism of PPARβ/δ on choroidal neovascularization using a laser-induced CNV model. Antagonism of PPARβ/δ provided a therapeutic effect on laser-induced lesion, whereas ligand activation of PPARβ/δ had no effect, as results obtained from former *in vitro* analyses [65].

3.4. Optic neuritis and related disorders

Optic neuritis (ON), a demyelinating, inflammatory disease of the optic nerve, could be the initial symptom of multiple sclerosis (MS) or appearing during the progression of the disease. At any stage, approximately half of MS patients develop the optic neuritis. An idiopathic demyelinating disorder of the optic nerve also occurs as Neuro Myelitis Optica (NMO) or Devic's disease, which is described by the co-occurrence of typically bilateral and severe optic neuritis with spinal cord involvement and the presence of a highly specific serum autoantibody (NMO-IgG), identifying the transmembrane channel Aquaporin 4. The restrictions between NMO and MS are relatively imprecise, from both the pathological and the clinical points of view and it is still a matter of controversy whether NMO has to be considered a variant of MS or a separate entity [66].

In view of their role in inflammation, the possible therapeutic efficacy of PPARγ agonists has been examined in experimental autoimmune encephalomyelitis (EAE), an *in vivo* model of MS, in which the autoimmune reaction against myelin is provoked in animals by active sensitization with myelin components. Even though numerous criticisms have been raised towards this model, EAE still offers an advantageous tool to ameliorate our knowledge about the treatment and pathogenesis of MS. Moreover, EAE is considered a relevant model to better understand the demyelinated diseases of the optic nerve [25]. A supplementary *in vivo* model is represented by T-cell receptor transgenic mice specific for myelin oligodendrocyte glycoprotein (MOG). These mice showed isolated optic neuritis either after sensitization or spontaneously with sub-optimal doses of MOG [67]. Therapeutic efficacy of PPARγ ligands has been shown in terms of improvement or suppression of clinical symptoms and reduction of inflammatory symptoms. Even though the anti-inflammatory activities of PPARγ agonists are multifaceted and intricate, various evidence has been provided indicating a direct action of PPARγ agonists on microglia/mononuclear phagocytic cells. In fact, participating in both adaptive and innate immune responses, microglia and mononuclear phagocytes are extremely implicated in the complex inflammatory signalling linked with MS. Their role has been extensively and recently reviewed [68, 69]. The PPARγ natural agonist, 15d-PGJ2 [70] and the PPARα agonist, gemfibrozil [71] were indicated to considerably reduce macrophage infiltration in the site of lesion. Smaller number of IL1β-positive cells were noticed in the EAE brain of mice treated with GW0742, a PPARδ agonist, and this finding was considered indicative of a decrease of glial

activation [72]. PPARγ inhibition of microglial cell activation is also sustained by *in vitro* experiments [70–75].

3.5. Glaucoma

Glaucomas are a group of optic neuropathies characterized by progressive degeneration of retinal ganglion cells. These are central nervous system neurons that have their cell bodies in the inner retina and axons in the optic nerve. Degeneration of these nerves results in *cupping*, a characteristic appearance of the optic disc and visual loss. The biological basis of glaucoma is poorly understood and the factors contributing to its progression have not been fully characterized [76, 77].

Glaucoma is one of the main cause of blindness in the world, which lead to retinal nerve fiber layer alterations; optic nerve head cupping; and typical visual field defect [78]. Elevated intraocular pressure (IOP) has been recognized as the major risk factor for the development of glaucoma and the only modifiable factor associated with the disease [79]. Convincing evidence indicates that an early insult occurs to retinal ganglion cell (RGC) axons at the optic nerve head and ultimately degenerate but the mechanism is still unclear, although early neuroinflammatory responses seem to suggest a role of inflammation in glaucoma pathology [80, 81].

Lipid messengers and endocannabinoids from the PEA (Palmitoylethanolamide) family are synthesized in ocular tissue and have been identified as intraocular pressure reducing compounds [81]. PEA safety and efficacy have been evaluated in different clinical trials of inflammatory conditions and chronic pain states, including glaucoma. Due to the convergent pathogenetic pathways related to retinal glia activation, PEA holds a promise for both glaucoma as well as diabetic retinopathy [81]. PEA is a pleiotropic naturally occurring endogenous N-acetylethanolamine that plays an important biological role in many living organisms, including humans [81]. PEA's beneficial effects are dose-dependent and mediated through various receptors, such as PPARα, PPARγ, PPARβ, GPR 119, and TRPV1. PEA is known to down-regulate proinflammatory genes and possess a broad anti-inflammatory, antioxidant, and cytoprotective activities. As both glaucoma and diabetic retinopathy share a common pathogenetic pathway, PEA should be considered in the treatment and prophylaxis of retinal damage in both disorders [81].

Different studies have pointed to the putative retina-protective properties of PEA, through the modulation of PPARs, especially the PPARα. Recently, it has been described as PEA is able to inhibit the induction of the proinflammatory genes, such as IL-1b, CCL4, and NOS2 and adhesion molecules, such as ICAM-1 and P-selectin. CCL4 can induce monocyte migration and this migration is also blocked by PEA [82].

PPARα as well as PEA are localized in nervous tissue and their expression may show substantial changes during pathological conditions. Currently, there is a consensus in the literature regarding the idea that the PPAR family is one of the primary targets of PEA. Through activation of the PPARs, especially PPARα, PEA is attenuating proinflammatory mediators and/or increasing anti-inflammatory mediators [81, 82]. The role of PEA is not limited only to PPARα pathway, but different targets, such as PPARβ and PPARγ, play an additional role. In fact, in a study conducted on spinal cord injured mice it was demonstrated that PEA treatment induced a limited infiltration of inflammatory cells, a protective effect that was attenuated after

treatment with PPARγ and PPARβ antagonists. PEA increases PPARα and PPARγ expression and consequently eliminates any neuroinflammatory processes induced by the antagonists of these receptors [83].

3.6. Ocular injuries

The cornea is the ocular surface exerting protective role against external agents being transparent to enable the transmission of light. Chemical burns can alter this barrier [82], and in addition to corneal injury and eyelid burns, are risk factors for ocular complications, including ulcers, scars and neovascularization (NV) [83, 84].

Chemical burns can be divided into alkali and acid burns, with corneal alkali burns (CAB) frequently resulting in a greater severity of injury [85]. As previously stated, PPARs play a role in the control of a variety of inflammatory, angiogenic and also fibrotic physiological processes [22].

The irregular remodeling of matrix structures may lead to scar formation. Scarring is due to the high proliferation of inflammatory cells and fibroblasts during burn wound healing [86].

Corneal fibrosis can result in visual impairment and blindness. It has been detected that alkali burned corneas exhibit obvious interfibrillar distances with greater levels of the fibrotic marker α-smooth muscle actin (αSMA) [87]. TGFβ-induced differentiation of corneal fibroblasts to myofibroblasts could be avoided [88]. During healing, in the injured tissue of a CAB model, it has been observed an important increase of inflammation and scarring/fibrosis. The prognosis of CAB is dependent upon ocular surface inflammation and the scarring and fibrosis of the cornea and eyelid [89]. PPARγ possess strong anti-fibrotic properties in the cornea and several other types of tissue, with PPARγ ligands blocking αSMA induction [90]. Some studies have demonstrated that treating with ophthalmic solutions of PPARγ agonists, the fibrotic reaction is reduced in the early phase post-CAB and in additional fibrotic pathologies [89–92].

3.7. Thyroid eye disease

PPARγ has been found to be associated with thyroid eye disease (TED), an autoimmune disorder in which severe inflammation induces to orbital tissue remodelling, among which the accumulation of extracellular macromolecules and fat. Disease progression is determined by interactions between orbital fibroblasts and lymphocytes. These cells are involved in a cycle of mutual activation, which induces the tissue characteristics of TED. It has been demonstrated that PPARγ levels are higher in orbital tissue from patients with active TED than in controls or individuals with inactive TED [93].

PPARγ activation is critical to adipogenesis, making it a potential culprit in the pathological fat accumulation associated with TED. Downregulation of PPARγ could reduce adipogenesis [94]. Starkey and collaborators reported that a male type 2 diabetic patient, treated with pioglitazone, experienced rapid exacerbation of his TED, which had been stable and inactive for more than 2 yr. In his in vitro experiments, by isolating and culturing preadipocytes from TED orbits, he demonstrated that the PPARγ agonists resulted in a 2- to 13-fold increase, and a PPARγ antagonist produced a 2- to 7-fold reduction in adipogenesis [95].

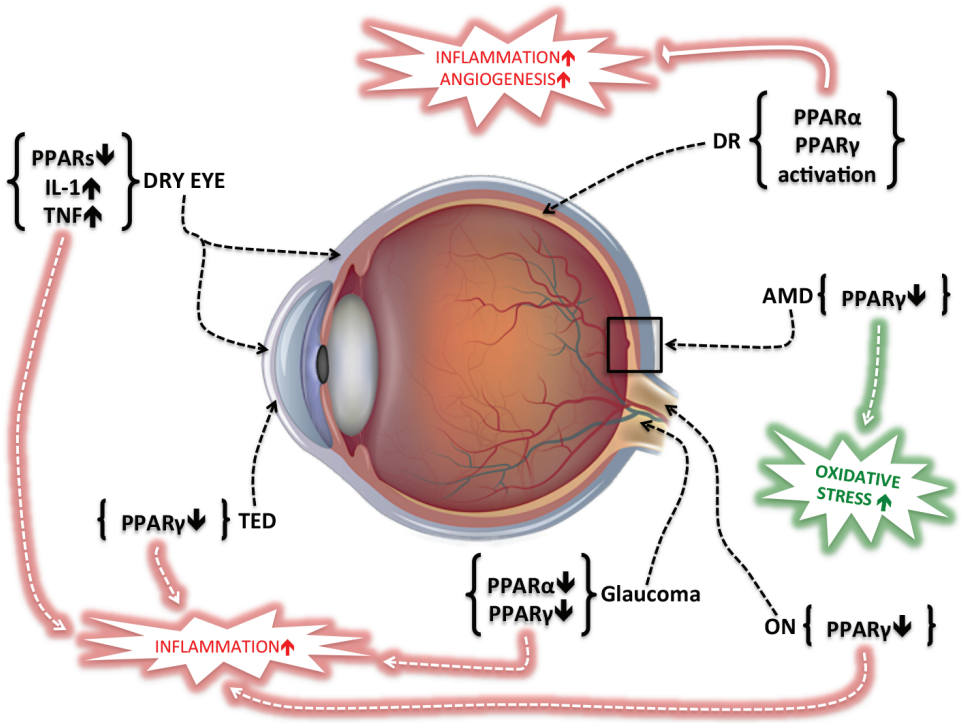

Figure 1: Summary of PPARs presence and modulation in different ocular pathologies.

However, PPARγ also has anti-inflammatory activity. The anti-inflammatory potential of PPARγ can significantly affect TED since this transcription factor has been identified in orbital tissues from TED patients and since its activity may be involved in the regulation of IFNγ-induced chemokine expression; moreover, it has been reported that its activators might attenuate the recruitment of activated T-lymphocytes to sites of inflammation [96, 97]. Together, the evidence indicates that PPARγ ligands may interrupt communication between mononuclear cells and fibroblasts [95]. Nevertheless, PPARγ ligands can also promote T lymphocyte synthesis of IL-8. Consequently, the effects of PPARγ on T-lymphocytes are complex and require additional study. In particular, Pioglitazone and rosiglitazone have been found to inhibit TGFβ-induced, hyaluronan-dependent, T-cell adhesion to orbital fibroblasts, suggesting that they could inhibit intense inflammation and might be useful in treating TED [98].

4. Conclusion

PPARs are present in the eye with different localization and different abundance, depending on the specific isotype. Their role in the regulation of inflammatory process has suggested their possible action in regulating inflammation and oxidative stress in ocular pathologies (Figure 1). PPAR γ and its ligands were the most studied in eye diseases. TZDs (i.e., pioglitazone, troglitazone, and rosiglitazone) and 15d-PGJ2, are the existing therapeutic agents targeted to activate PPARγ and may represent innovative adjuvants in the treatment of ocular pathologies. In fact, as previously described, since inflammation is a crucial event in the eye diseases, it has been proposed that PPARγ ligands may have therapeutic effects by modulating inflammation, other than providing glycemic control [37]; in addition, these results concur to novel genomic

Table 1: Summary of PPAR ligands in different ocular diseases.

Pathology	Area affected	Nuclear receptor target therapy	Therapies		Ref.
Diabetic Retinopathy	*Retina (Macula)*	PPARγ	TZD:	↑ PPARγ	[22–31, 39–42];
		PPARβ	GW501516:	↑ VEGF	[48];
		PPARα	Fenofibrate:	↑ PPARα	[52, 53].
Dry eye	*Cornea Conjunctiva*	PPARs	Pioglitazone:	↑PPAR	[54, 55].
				↓ NO	
Age-Related Macular Degeneration	*Retina (Macula)*	PPARγ	Troglitazone:	↓ Oxidative Stress	
			15d-PGJ2:	↓ Oxidative Stress	[56–65].
		PPARβ			
		PPARα			
Optic Neuritis	*Optic Nerve*	PPARγ	PPARγ	↑ PPARγ	[66–75].
			agonists:	↓ TNF	
Glaucoma	*Optic Nerve*	PPARs	PEA	↑ PPARγ	[76–83].
				↑ PPARα	
Ocular injuries	*Cornea*	PPARs	PPARγ	↑ PPARγ	[83–92].
			agonists:	↓ fibrotic reaction	
Thyroid eye disease	*Cornea*	PPARγ	Glitazones:	↓ Inflammation	[93–98].

information that therapeutic targeting of PPARγ with a known PPARγ ligand, the TZD rosiglitazone, can diminish the progression of different ocular pathologies. For example, Pioglitazone and 15d-PGJ2 may inhibit corneal neovascularization and, interestingly, in retinal diseases troglitazone and rosiglitazone may attenuate the progression of AMD and DR *in vivo* or impact glaucoma or CAB.

In summary, several experimental studies and numerous clinical studies have offered evidences that PPARs, particularly the γ isoform, may represent a potential target for therapy that may be used as treatment of ocular pathologies. Nevertheless, the complexity of PPARs activation other than supporting positive effects, may present undesirable side-effects. Further preclinical and clinical trials are necessary to determine the efficacy and to demonstrate the safety of these drugs for the treatment of ocular pathologies.

Competing Interests

The authors declare no competing interests.

References

[1] P. Tontonoz and B. M. Spiegelman, "Fat and beyond: the diverse biology of PPARγ," *Annual Review of Biochemistry*, vol. 77, pp. 289–312, 2008.

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

[3] Y. Zhu, K. Alvares, Q. Huang, M. S. Rao, and J. K. Reddy, "Cloning of a new member of the peroxisome proliferator-activated receptor gene family from mouse liver," *The Journal of Biological Chemistry*, vol. 268, no. 36, pp. 26817–26820, 1993.

[4] F. Chen, S. W. Law, and B. W. O'Malley, "Identification of two mPPAR related receptors and evidence for the existence of five subfamily members," *Biochemical and Biophysical Research Communications*, vol. 196, no. 2, pp. 671–677, 1993.

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

[6] X. Xin, S. Yang, J. Kowalski, and M. E. Gerritsen, "Peroxisome proliferator-activated receptor γ ligands are potent inhibitors of angiogenesis *in vitro* and in vivo," *The Journal of Biological Chemistry*, vol. 274, no. 13, pp. 9116–9121, 1999.

[7] J. V. Jester and D. J. Brown, "Wakayama symposium: peroxisome proliferator-activated receptor-gamma (PPARgamma) and meibomian gland dysfunction," *The Ocular Surface*, vol. 10, no. 4, pp. 224–229, 2012.

[8] M. K. Song, B. D. Roufogalis, and T. H. W. Huang, "Modulation of diabetic retinopathy pathophysiology by natural medicines through PPAR-γ-related pharmacology," *British Journal of Pharmacology*, vol. 165, no. 1, pp. 4–19, 2012.

[9] L. L. C. Poulsen, M. Siersbaek, and S. Mandrup, "PPARs: fatty acid sensors controlling metabolism," *Seminars in Cell & Developmental Biology*, vol. 23, no. 6, pp. 631–639, 2012.

[10] M. Abdelrahman, A. Sivarajah, and C. Thiemermann, "Beneficial effects of PPAR-gamma ligands in ischemia-reperfusion injury, inflammation and shock," *Cardiovascular Research*, vol. 65, no. 4, pp. 772–781, 2005.

[11] S. van Neerven and J. Mey, "RAR/RXR and PPAR/RXR signaling in spinal cord injury," *PPAR Research*, vol. 2007, Article ID 29275, 14 pages, 2007.

[12] R. T. Nolte, G. B. Wisely, S. Westin et al., "Ligand binding and co-activator assembly of the peroxisome proliferator- activated receptor-γ," *Nature*, vol. 395, no. 6698, pp. 137–143, 1998.

[13] B. Cariou, B. Charbonnel, and B. Staels, "Thiazolidinediones and PPARγ agonists: time for a reassessment," *Trends in Endocrinology & Metabolism*, vol. 23, no. 5, pp. 205–215, 2012.

[14] J. Kung and R. R. Henry, "Thiazolidinedione safety," *Expert Opinion on Drug Safety*, vol. 11, no. 4, pp. 565–579, 2012.

[15] J. M. Olefsky and A. R. Saltiel, "PPARγ and the treatment of insulin resistance," *Trends in Endocrinology & Metabolism*, vol. 11, no. 9, pp. 362–368, 2000.

[16] R. F. Kletzien, S. D. Clarke, and R. G. Ulrich, "Enhancement of adipocyte differentiation by an insulin-sensitizing agent," *Molecular Pharmacology*, vol. 41, no. 2, pp. 393–398, 1992.

[17] A. A. Herzlich, X. Ding, D. Shen, R. J. Ross, J. Tuo, and C. C. Chan, "Peroxisome proliferator-activated receptor expression in murine models and humans with age-related macular degeneration," *The Open Biology Journal*, vol. 2, no. 1, pp. 141–148, 2009.

[18] M. A. Dwyer, D. Kazmin, P. Hu, D. P. McDonnell, and G. Malek, "Research resource: nuclear receptor atlas of human retinal pigment epithelial cells: potential relevance to age-related macular degeneration," *Molecular Endocrinology*, vol. 25, no. 2, pp. 360–372, 2011.

[19] S. Qin, A. P. McLaughlin, and G. W. de Vries, "Protection of RPE cells from oxidative injury by 15-deoxy-Δ 12,14-prostaglandin J2 by augmenting GSH and activating MAPK," *Investigative Ophthalmology & Visual Science*, vol. 47, no. 11, pp. 5098–5105, 2006.

[20] A. Ciudin, C. Hernández, and R. Simó, "Molecular implications of the PPARS in the diabetic eye," *PPAR Research*, 2013.

[21] J. M. Zhu JM and N. Hu, "Expression of peroxisome proliferator-activated receptor γ in rat retina during development," *Int J Ophthalmol*, vol. 18, no. 8, pp. 52–56, 2015.

[22] Su Zhang, Hongwei Gu, and Nan Hu, "Role of Peroxisome Proliferator-Activated Receptor γ in Ocular Diseases," *Journal of Ophthalmology*, vol. 2015, Article ID 275435, 10 pages, 2015.

[23] G. A. Rodrigues, F. Maurier-Mahé, D.-L. Shurland et al., "Differential effects of PPARγ ligands on oxidative stress-induced death of retinal pigmented epithelial cells," *Investigative Ophthalmology & Visual Science*, vol. 52, no. 2, pp. 890–903, 2011.

[24] A. Stahl, P. Sapieha, K. M. Connor et al., "Short communication: PPARγ mediates a direct antiangiogenic effect of ω3-PUFAs in proliferative retinopathy," *Circulation Research*, vol. 107, no. 4, pp. 495–500, 2010.

[25] J. Zhu, J. Zhang, M. Ji et al., "The role of peroxisome proliferator-activated receptor and effects of its agonist, pioglitazone, on a rat model of optic nerve crush: PPARgamma in retinal neuroprotection," *PLoS ONE*, vol. 8, no. 7, Article ID e68935, 2013.

[26] X.-Y. Zhang, Y.-Q. Xiao, Y. Zhang, and W. Ye, "Protective effect of pioglitazone on retinal ischemia/ reperfusion injury in rats," *Investigative Ophthalmology & Visual Science*, vol. 54, no. 6, pp. 3912–3921, 2013.

[27] J. Y. Chang, P. S. Bora, and N. S. Bora, "Prevention of oxidative stress-induced retinal pigment epithelial cell death by the PPARγ agonists, 15-deoxy-delta 12, 14-prostaglandin J 2," *PPAR Research*, 2008.

[28] S. Polvani, M. Tarocchi, and A. Galli, "PPAR and oxidative stress: con(β) catenating NRF2 and FOXO," *PPAR Research*, vol. 2012, Article ID 641087, 15 pages, 2012.

[29] M. Sokolowska, M. L. Kowalski, and R. Pawliczak, "pp. AR-Agamma) and their role in immunoregulation and inflammation control," *Postępy Higieny i Medycyny Doświadczalnej*, vol. 59, pp. 472–484, 2005.

[30] M. A. Sarayba, L. Li, T. Tungsiripat et al., "Inhibition of corneal neovascularization by a peroxisome proliferator-activated receptor-γ ligand," *Experimental Eye Research*, vol. 80, no. 3, pp. 435–442, 2005.

[31] H. A. Pershadsingh and D. M. Moore, "PPARγ agonists: Potential as therapeutics for neovascular retinopathies," *PPAR Research*, 2008.

[32] D. Bishop-Bailey and J. Bystrom, "Emerging roles of peroxisome proliferator-activated receptor-β/δ in inflammation," *Pharmacology & Therapeutics*, vol. 124, no. 2, pp. 141–150, 2009.

[33] David Bishop-Bailey, "A Role for PPARβ/δ in Ocular Angiogenesis," *PPAR Research*, vol. 2008, Article ID 825970, 6 pages, 2008.

[34] J. Zhang and K. W. Ward, "WY-14 643, a Selective PPARα Agonist, Induces Proinflammatory and Proangiogenic Responses in Human Ocular Cells," *International Journal of Toxicology*, vol. 29, no. 5, pp. 496–504, 2010.

[35] E. A. Pearsall, R. Cheng, K. Zhou et al., "AR-Ais essential for retinal lipid metabolism and neuronal survival," *BMC Biol*, vol. 15, no. 1, p. 113, 2017.

[36] V. Costa and A. Ciccodicola, "Is PPARG the key gene in diabetic retinopathy?" *British Journal of Pharmacology*, vol. 165, no. 1, pp. 1–3, 2012.

[37] K. Muranaka, Y. Yanagi, Y. Tamaki et al., "Effects of peroxisome proliferator-activated receptor γ and its ligand on blood-retinal barrier in a streptozotocin-induced diabetic model," *Investigative Ophthalmology & Visual Science*, vol. 47, no. 10, pp. 4547–4552, 2006.

[38] N. Toda and M. Nakanishi-Toda, "Nitric oxide: ocular blood flow, glaucoma, and diabetic retinopathy," *Progress in Retinal and Eye Research*, vol. 26, no. 3, pp. 205–238, 2007.

[39] L. Q. Shen, A. Child, G. M. Weber, J. Folkman, and L. P. Aiello, "Rosiglitazone and delayed onset of proliferative diabetic retinopathy," *JAMA Ophtalmology*, vol. 126, no. 6, pp. 793–799, 2008.

[40] I. Idris, G. Warren, and R. Donnelly, "Association between thiazolidinedione treatment and risk of macular edema among patients with type 2 diabetes," *JAMA Internal Medicine*, vol. 172, no. 13, pp. 1005–1011, 2012.

[41] W. T. Ambrosius, "Lack of Association Between Thiazolidinediones and Macular Edema in Type 2 Diabetes," *JAMA Ophtalmology*, vol. 128, no. 3, p. 312, 2010.

[42] T. Baba, K. Shimada, S. Neugebauer, D. Yamada, S. Hashimoto, and T. Watanabe, "The oral insulin sensitizer, thiazolidinedione, increases plasma vascular endothelial growth factor in type 2 diabetic patients," *Diabetes Care*, vol. 24, no. 5, pp. 953–954, 2001.

[43] S. Azar, G. M. El-Mollayess, L. Al Shaar, H. I. Salti, and Z. F. Bashshur, "Impact of thiazolidinediones on macular thickness and volume in diabetic eyes," *Canadian Journal of Ophthalmology*, vol. 48, no. 4, pp. 312–316, 2013.

[44] S. Asgary, G. A. Naderi, N. Sarraf-Zadegan, and R. Vakili, "The inhibitory effects of pure flavonoids on in vitro protein glycosylation," *Journal of Herbal Pharmacotherapy*, vol. 2, no. 2, pp. 47–55, 2002.

[45] H. Y. Wang and M. L. Cheng, "Effects of Dan-shao-huaxian on expression of, pp. AR-Agamma and NF-kappa," in *Proceedings of the B in rat liver fibrosis*, vol. 7, pp. 179–184, 2008.

[46] R. J. Herm, "Age-related macular degeneration," *The New England Journal of Medicine*, vol. 359, no. 16, pp. 1735–1736, 2008.

[47] F. Yang, J. Yu, F. Ke et al., "Curcumin Alleviates Diabetic Retinopathy in Experimental Diabetic Rats," *Ophthalmic Research*, vol. 60, no. 1, pp. 43–54, 2018.

[48] Guangjie Liu, Xuan Li, Yan Li et al., "PPARδ Agonist GW501516 Inhibits PDGF-Stimulated Pulmonary Arterial Smooth Muscle Cell Function Related to Pathological Vascular Remodeling," *BioMed Research International*, vol. 2013, Article ID 903947, 8 pages, 2013.

[49] B. P. Harrold, V. J. Marmion, and K. R. Gough, "A double-blind controlled trial of clofibrate in the treatment of diabetic retinopathy.," *Diabetes*, vol. 18, no. 5, pp. 285–291, 1969.

[50] P. A. Dorne, "Exudative diabetic retinopathy. The use of clofibrate in the treatment of hard exudates using a reduced but prolonged dosage over several years," *Archives d'Ophtalmologie et Revue Generale d'Ophtalmologie*, vol. 37, no. 5, pp. 393–400, 1977.

[51] Y. Hu, Y. Chen, L. Ding et al., "Pathogenic role of diabetes-induced PPAR-α down-regulation in microvascular dysfunction," *Proceedings of the National Acadamy of Sciences of the United States of America*, vol. 110, no. 38, pp. 15401–15406, 2013.

[52] A. D. Wright and P. M. Dodson, "Medical management of diabetic retinopathy: Fenofibrate and ACCORD Eye studies," *Eye*, vol. 25, no. 7, pp. 843–849, 2011.

[53] A. Keech, P. Mitchell, P. Summanen et al., "Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial," *The Lancet*, vol. 370, no. 9600, pp. 1687–1697, 2007.

[54] Y. Chen, X. Zhang, L. Yang et al., "Decreased PPAR-γ expression in the conjunctiva and increased expression of TNF-α and IL-1β in the conjunctiva and tear fluid of dry eye mice," *Molecular Medicine Reports*, vol. 9, no. 5, pp. 2015–2023, 2014.

[55] C. Beauregard and P. C. Brandt, "Peroxisome proliferator-activated receptor agonists inhibit interleukin-1beta-mediated nitric oxide production in cultured lacrimal gland acinar cells," *Journal of Ocular Pharmacology and Therapeutics*, vol. 19, no. 6, pp. 579–587, 2003.

[56] S. L. Fine, J. W. Berger, M. G. Maguire, and A. C. Ho, "Age-related macular degeneration," *The New England Journal of Medicine*, vol. 342, no. 7, pp. 483–492, 2000.

[57] T. A. Ciulla, A. Harris, and B. J. Martin, "Ocular perfusion and age-related macular degeneration," *Acta Ophthalmologica Scandinavica*, vol. 79, no. 2, pp. 108–115, 2001.

[58] T. Murata, Y. Hata, T. Ishibashi et al., "Response of experimental retinal neovascularization to thiazolidinediones," *JAMA Ophtalmology*, vol. 119, no. 5, pp. 709–717, 2001.

[59] J. P. Vanden Heuvel, "Nutrigenomics and nutrigenetics of ω3 polyunsaturated fatty acids," *Progress in Molecular Biology and Translational Science*, vol. 108, pp. 75–112, 2012.

[60] E. W.-T. Chong, A. J. Kreis, T. Y. Wong, J. A. Simpson, and R. H. Guymer, "Dietary omega-3 fatty acid and fish intake in the primary prevention of age-related macular degeneration: a systematic review and meta-analysis," *JAMA Ophtalmology*, vol. 126, no. 6, pp. 826–833, 2008.

[61] J. Cai, J. Cai, K. C. Nelson et al., "Oxidative damage and protection of the RPE," *Progress in Retinal and Eye Research*, vol. 19, no. 2, pp. 205–221, 2000.

[62] J. P. SanGiovanni and E. Y. Chew, "The role of omega-3 long-chain polyunsaturated fatty acids in health and disease of the retina," *Progress in Retinal and Eye Research*, vol. 24, no. 1, pp. 87–138, 2005.

[63] T. K. Garg and J. Y. Chang, "Oxidative stress causes ERK phosphorylation and cell death in cultured retinal pigment epithelium: prevention of cell death by AG126 and 15-deoxy-delta 12, 14-PGJ2," *BMC Ophthalmology*, vol. 3, article 5, 2003.

[64] M. Choudhary, J. Ding, X. Qi et al., "PPARβ/δ selectively regulates phenotypic features of age-related macular degeneration," *AGING*, vol. 8, no. 9, pp. 1952–1978, 2016.

[65] P. L. Feldman, M. H. Lambert, and B. R. Henke, "PPAR modulators and PPAR pan agonists for metabolic diseases: The next generation of drugs targeting peroxisome proliferator-activated receptors?" *Current Topics in Medicinal Chemistry*, vol. 8, no. 9, pp. 728–749, 2008.

[66] R. Marignier, A. Nicolle, C. Watrin et al., "Oligodendrocytes are damaged by neuromyelitis optica immunoglobulin G via astrocyte injury," *Brain*, vol. 133, no. 9, pp. 2578–2591, 2010.

[67] E. Bettelli, M. Pagany, H. L. Weiner, C. Linington, R. A. Sobel, and V. K. Kuchroo, "Myelin oligodendrocyte glycoprotein-specific T cell receptor transgenic mice develop spontaneous autoimmune optic neuritis," *The Journal of Experimental Medicine*, vol. 197, no. 9, pp. 1073–1081, 2003.

[68] S. Dhib-Jalbut, "Pathogenesis of myelin/oligodendrocyte damage in multiple sclerosis," *Neurology*, vol. 68, no. 22, pp. S13–S21, 2007.

[69] P. Sanders and J. De Keyser, "Janus faces of microglia in multiple sclerosis," *Brain Research Reviews*, vol. 54, no. 2, pp. 274–285, 2007.

[70] A. Diab, R. Z. Hussain, A. E. Lovett-Racke, J. A. Chavis, P. D. Drew, and M. K. Racke, "Ligands for the peroxisome proliferator-activated receptor-γ and the retinoid X receptor exert additive anti-inflammatory effects on experimental autoimmune encephalomyelitis," *Journal of Neuroimmunology*, vol. 148, no. 1-2, pp. 116–126, 2004.

[71] M. Meissner, M. Stein, C. Urbich et al., "PPARalpha activators inhibit vascular endothelial growth factor receptor-2 expression by repressing Sp1-dependent DNA binding and transactivation," *Circulation Research*, vol. 94, no. 3, pp. 324–332, 2004.

[72] L. Piqueras, A. R. Reynolds, K. M. Hodivala-Dilke et al., "Activation of PPARβ/δ induces endothelial cell proliferation and angiogenesis," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 27, no. 1, pp. 63–69, 2007.

[73] A. Bernardo, G. Levi, and L. Minghetti, "Role of the peroxisome proliferator-activated receptor-γ (PPAR-γ) and its natural ligand 15-deoxy-Δ12,14-prostaglandin J2 in the regulation of microglial functions," *European Journal of Neuroscience*, vol. 12, no. 7, pp. 2215–2223, 2000.

[74] P. D. Storer, J. Xu, J. Chavis, and P. D. Drew, "Peroxisome proliferator-activated receptor-gamma agonists inhibit the activation of microglia and astrocytes: implications for multiple sclerosis," *Journal of Neuroimmunology*, vol. 161, no. 1-2, pp. 113–122, 2005.

[75] J. Xu and P. D. Drew, "Peroxisome proliferator-activated receptor-γ agonists suppress the production of IL-12 family cytokines by activated glia," *The Journal of Immunology*, vol. 178, no. 3, pp. 1904–1913, 2007.

[76] R. N. Weinreb and P. Tee Khaw, "Primary open-angle glaucoma," *The Lancet*, vol. 363, no. 9422, pp. 1711–1720, 2004.

[77] R. W. Nickells, G. R. Howell, I. Soto, and S. W. M. John, "Under pressure: cellular and molecular responses during glaucoma, a common neurodegeneration with axonopathy," *Annual Review of Neuroscience*, vol. 35, pp. 153–179, 2012.

[78] C. Costagliola, R. Dell'Omo, M. R. Romano, M. Rinaldi, L. Zeppa, and F. Parmeggiani, "Pharmacotherapy of intraocular pressure: Part I. Parasympathomimetic, sympathomimetic and sympatholytics," *Expert Opinion on Pharmacotherapy*, vol. 10, no. 16, pp. 2663–2677, 2009.

[79] A. L. Coleman and S. Miglior, "Risk factors for glaucoma onset and progression," *Survey of Ophthalmology*, vol. 53, no. 6, pp. S3–S10, 2008.

[80] I. Soto and G. R. Howell, "The complex role of neuroinflammation in glaucoma," *Cold Spring Harbor Perspectives in Medicine*, vol. 4, no. 8, p. 14, 2014.

[81] J. M. Keppel Hesselink, C. Costagliola, J. Fakhry, and D. J. Kopsky, "Palmitoylethanolamide, a Natural Retinoprotectant: Its Putative Relevance for the Treatment of Glaucoma and Diabetic Retinopathy," *Journal of Ophthalmology*, vol. 2015, 2015.

[82] R. di Paola, D. Impellizzeri, A. Torre et al., "Effects of palmitoylethanolamide on intestinal injury and inflammation caused by ischemia-reperfusion in mice," *Journal of Leukocyte Biology*, vol. 91, no. 6, pp. 911–920, 2012.

[83] I. Paterniti, D. Impellizzeri, R. Crupi et al., "Molecular evidence for the involvement of PPAR-delta and PPAR-gamma in anti-inflammatory and neuroprotective activities of palmitoylethanolamide after spinal cord trauma," *Journal of Neuroinflammation*, vol. 10, article 20, 2013.

[84] Y.-Y. Leong and L. Tong, "Barrier function in the ocular surface: From conventional paradigms to new opportunities," *The Ocular Surface*, vol. 13, no. 2, pp. 103–109, 2015.

[85] M. S. Cabalag, J. Wasiak, Q. Syed, E. Paul, A. J. Hall, and H. Cleland, "Early and late complications of ocular burn injuries," *Journal of Plastic, Reconstructive & Aesthetic Surgery*, vol. 68, no. 3, pp. 356–361, 2015.

[86] S. Saika, O. Yamanaka, Y. Okada et al., "Effect of overexpression of pparγ on the healing process of corneal alkali burn in mice," *American Journal of Physiology-Cell Physiology*, vol. 293, no. 1, pp. C75–C86, 2007.

[87] K. M. Gronkiewicz, E. A. Giuliano, K. Kuroki et al., "Development of a novel in vivo corneal fibrosis model in the dog," *Experimental Eye Research*, vol. 143, pp. 75–88, 2016.

[88] K. S. Donnelly, E. A. Giuliano, A. Sharma, and R. R. Mohan, "Suberoylanilide hydroxamic acid (vorinostat): Its role on equine corneal fibrosis and matrix metalloproteinase activity," *Veterinary Ophthalmology*, vol. 17, no. 1, pp. 61–68, 2014.

[89] Q. Zhou, L. Yang, M. Qu et al., "Role of senescent fibroblasts on alkali-induced corneal neovascularization," *Journal of Cellular Physiology*, vol. 227, no. 3, pp. 1148–1156, 2012.

[90] K.-I. Jeon, R. P. Phipps, P. J. Sime, and K. R. Huxlin, "Inhibitory effects of PPARγ ligands on TGF-β1-induced CTGF expression in cat corneal fibroblasts," *Experimental Eye Research*, vol. 138, pp. 52–58, 2015.

[91] Y.-S. Yoon, S.-Y. Kim, M.-J. Kim, J.-H. Lim, M.-S. Cho, and J. L. Kang, "PPARγ activation following apoptotic cell instillation promotes resolution of lung inflammation and fibrosis via regulation of efferocytosis and proresolving cytokines," *Mucosal Immunology*, vol. 8, no. 5, pp. 1031–1046, 2015.

[92] H. Luo, H. Zhu, B. Zhou, X. Xiao, and X. Zuo, "MicroRNA-130b regulates scleroderma fibrosis by targeting peroxisome proliferator-activated receptor γ," *Modern Rheumatology*, vol. 25, no. 4, pp. 595–602, 2015.

[93] G. M. Lehmann, S. E. Feldon, T. J. Smith, and R. P. Phipps, "Immune mechanisms in thyroid eye disease," *Thyroid*, vol. 18, no. 9, pp. 959–965, 2008.

[94] L. Y. Mimura, S. M. F. Villares, M. L. R. Monteiro, I. C. Guazzelli, and W. Bloise, "Peroxisome proliferator-activated receptor-γ gene expression in orbital adipose/connective tissues is increased during the active stage of Graves' ophthalmopathy," *Thyroid*, vol. 13, no. 9, pp. 845–850, 2003.

[95] K. Starkey, A. Heufelder, G. Baker et al., "Peroxisome proliferator-activated receptor-γ in thyroid eye disease: contraindication for thiazolidinedione use?" *The Journal of Clinical Endocrinology & Metabolism*, vol. 88, no. 1, pp. 55–59, 2003.

[96] T. Shibata, M. Kondo, T. Osawa, N. Shibata, M. Kobayashi, and K. Uchida, "15-deoxy-delta 12,14-prostaglandin J2. A prostaglandin D2 metabolite generated during inflammatory processes," *The Journal of Biological Chemistry*, vol. 277, no. 12, pp. 10459–10466, 2002.

[97] D. M. Ray, S. L. Spinelli, J. J. O'Brien, N. Blumberg, and R. P. Phipps, "Platelets as a novel target for PPARγ ligands: Implications for inflammation, diabetes, and cardiovascular disease," *BioDrugs*, vol. 20, no. 4, pp. 231–241, 2006.

[98] N. Guo, C. F. Woeller, S. E. Feldon, and R. P. Phipps, "Peroxisome proliferator-activated receptor γ ligands inhibit transforming growth factor-β-induced, hyaluronan-dependent, T cell adhesion to orbital fibroblasts," *The Journal of Biological Chemistry*, vol. 286, no. 21, pp. 18856–18867, 2011.