• Review Article •

Targeting oxidative stress and inflammation in diabetic retinopathy: the role of PPARs

Yi-Ge Zhang, Meng-Jiao Zhang, Mei Sun, Jing Xu, Li-Ke Xie, Xiao-Feng Hao

Department of Fundus Diseases and Ophthalmic Surgery, Eye Hospital, China Academy of Chinese Medical Sciences, Beijing 100040, China

Co-first Authors: Yi-Ge Zhang and Meng-Jiao Zhang

Correspondence to: Li-Ke Xie and Xiao-Feng Hao. Department of Fundus Diseases and Ophthalmic Surgery, Eye Hospital, China Academy of Chinese Medical Sciences, No.33 Lugu Road, Shijingshan District, Beijing 100040, China. bjxielike@sina.com; fmmuhao@163.com

Received: 2026-04-24 Accepted: 2026-06-12

Abstract

● Diabetic retinopathy (DR) is the leading cause of preventable blindness in working-age adults globally. Current therapies mainly target advanced vascular lesions, leaving early metabolic and inflammatory dysregulation unaddressed. Dysregulated lipid metabolism acts as a critical upstream initiator of DR, converging with oxidative stress and chronic inflammation to form a self-amplifying pathogenic loop driving retinal neurovascular degeneration. Peroxisome proliferator-activated receptors (PPARs) are master transcriptional regulators linking lipid metabolism, oxidative stress, and inflammation. This review systematically delineates the synergistic pathogenic network in DR, comprehensively discusses the pleiotropic retinal protective effects of PPARα and PPARγ, and summarizes the latest advances in PPAR-targeted nano-drug delivery systems that overcome the limitations of traditional agonists. Finally, we highlight key challenges and future directions to advance precision therapy for DR.

● **KEYWORDS:** diabetic retinopathy; peroxisome proliferator-activated receptors; retinal cholesterol homeostasis; oxidative stress; inflammation

DOI:10.18240/ijo.2026.11.19

Citation: Zhang YG, Zhang MJ, Sun M, Xu J, Xie LK, Hao XF. Targeting oxidative stress and inflammation in diabetic retinopathy: the role of PPARs. *Int J Ophthalmol* 2026;19(11):2265-2274

INTRODUCTION

Diabetes mellitus is a heterogeneous group of metabolic disorders characterized by chronic hyperglycemia. Chronic metabolic dysregulation leads to devastating macrovascular and microvascular complications, the leading causes of morbidity and mortality in diabetic patients[1]. Diabetic microangiopathy, traditionally considered the earliest and most prevalent chronic complication of diabetes, is now understood within the broader context of retinal neurovascular unit dysfunction, which involves the coordinated damage of microvascular, neural, and glial components[2].

Diabetic retinopathy (DR), a sight-threatening ocular complication, reflects this integrated retinal neurovascular unit injury and remains the leading cause of preventable blindness among working-age adults worldwide[3]. Sustained hyperglycemia induces cumulative retinal neurovascular unit damage, initiating a pathological cascade including blood-retinal barrier (BRB) disruption, retinal ischemia and hypoxia, neuroinflammation, and aberrant neovascularization, ultimately resulting in tractional retinal detachment and irreversible vision loss[4].

Over the past decade, substantial progress has been made in elucidating the complex molecular pathogenesis of DR. It is now well established that the reciprocal interaction between oxidative stress and chronic low-grade inflammation forms the central pathological network that propels DR development and progression, with dysregulated lipid metabolism acting as a critical upstream initiator. Given the rapidly escalating global burden of DR, identifying key molecular nodes linking lipid metabolic dyshomeostasis, oxidative stress, and inflammatory cascades, and translating these insights into safe and effective therapeutic, remain major unmet clinical needs and active research frontiers in both ophthalmology and endocrinology[5].

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated nuclear transcription factors and master regulators of glucose and lipid metabolism. Accumulating preclinical and clinical evidence indicates that PPARs exert pleiotropic protective effects in DR by targeting multiple pathological pathways[6]. In this review, we delineate the synergistic pathogenic roles of lipid dyshomeostasis, oxidative stress, and inflammation in DR. We then comprehensively discuss the central regulatory functions of PPARs in these interconnected pathological pathways, and provide an

overview of current understanding and promising directions for targeted DR prevention and treatment[7].

CORE PATHOLOGICAL ROLE OF DYSREGULATED LIPID METABOLISM IN DR

The retina is a metabolically demanding neural tissue with exceptionally high lipid content. Tight spatiotemporal lipid homeostasis is the fundamental to retinal structural integrity and physiological function. In diabetic, aberrant retinal cholesterol and fatty acid metabolism exerts dual detrimental effects: directly compromising retinal cell structural integrity and initiating a self-amplifying cascade of lipid peroxidation, oxidative stress, and chronic low-grade inflammation. Accumulating evidence establishes this metabolic dysregulation as a critical early initiating event in the pathogenesis of DR, preceding over vascular damage by years[8].

Dysregulation of the Retinal Cholesterol Homeostasis

Cholesterol is an essential structural and signaling lipid critical for cell membrane integrity, lipid raft formation, and intracellular signal transduction. In mammals, systemic cholesterol homeostasis is tightly regulated by coordinated synthesis, uptake, transport, and catabolism[9]. Uniquely, the retina maintains a largely autonomous cholesterol homeostasis network segregated from the systemic circulation by the BRB.

The BRB comprises two functionally distinct barriers that differentially regulate cholesterol trafficking. The inner BRB, formed by tight junctions between retinal capillary endothelial cells, is impermeable to circulating cholesterol under physiological conditions, isolating the neural retina from systemic cholesterol fluctuations. In contrast, the outer BRB, formed by a polarized monolayer of retinal pigment epithelium (RPE) cells, is selectively permeable to lipoproteins and serves as the exclusive gateway for circulating cholesterol entry into the retina[10]. Consistently, mouse lineage tracing studies have revealed that approximately 30% of total retinal sterols originate from systemic cholesterol uptake *via* the RPE. Circulating lipoprotein-associated cholesterol is first internalized by RPE cells through receptor-mediated endocytosis, followed by intracellular processing and vectorial transport to the neural retina[11-12].

Retinal cholesterol homeostasis is maintained by three interconnected processes: *de novo* biosynthesis, efflux and catabolic conversion. *De novo* cholesterol synthesis occurs in multiple retinal cell types, with the rate-limiting enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase abundantly expressed in the inner nuclear layer, outer nuclear layer, nerve fiber layer, and ganglion cell layer. Cholesterol efflux, the primary mechanism for removing excess intracellular cholesterol, is predominantly mediated by the adenosine triphosphate (ATP)-binding cassette transporters A1 (ABCA1) and ATP-binding cassette transporter G1 (ABCG1). These transporters transfer free cholesterol to lipid-poor apolipoprotein acceptors, primarily apolipoprotein A1, generating nascent high-density lipoprotein particles and initiating reverse cholesterol transport[13]. In polarized RPE cells, ABCA1 and ABCG1 localize to both apical and basolateral membranes, enabling bidirectional efflux. Apically effluxed cholesterol combines with apolipoprotein E to form lipoproteins that supply the neural retina, while basolaterally effluxed cholesterol returns to the choroidal circulation, preventing pathological accumulation[14-15].

The liver X receptor (LXR) pathway is the master transcriptional regulator of cellular cholesterol homeostasis. Excess intracellular cholesterol is converted to oxysterols, endogenous LXR agonists. Activated LXRs heterodimerize with retinoid X receptors and transcriptionally upregulate the expression of ABCA1 and ABCG1, establishing a negative feedback loop that tightly controls intracellular cholesterol levels[16].

In DR, this finely tuned network is profoundly disrupted. Impaired oxysterol generation and reduced LXRα transcriptional activity downregulate ABCA1 and ABCG1, leading to defective cholesterol efflux and subsequent intracellular and extracellular retinal cholesterol deposition. This creates a pro-atherogenic microenvironment resembling atherosclerotic plaques lipid rich necrotic cores, potently driving oxidative stress, chronic inflammation, and retinal damage[17-18].

Retinal Fatty Acid Metabolism Disorders and Retinal Injury Fatty acids are fundamental structural and functional components of continuously renewing retinal photoreceptor outer segments. Tight coordination of fatty acid synthesis, catabolism, and phospholipid remodeling is therefore indispensable for retinal neurons and vascular cell integrity and function[19-20].

In DR, retinal fatty acid metabolism is perturbed at multiple levels, causing direct retinal structural and functional damage[21]. Catabolically, mitochondrial fatty acid β-oxidation is markedly impaired, leading to reduced energy production and toxic lipid intermediate accumulation[22]. This is accompanied by a global reduction in *de novo* lipid biosynthetic capacity. Lipidomic analyses of diabetic rat retinas show a marked reduction in the long-chain to short-chain polyunsaturated fatty acids. Specifically, major glycerophospholipid (phosphatidylethanolamine, phosphatidylcholine, phosphatidylserine) and the essential omega-3 fatty acid docosahexaenoic acid are significantly decreased. These changes correlated with transcriptional downregulation of Elovl2 and Elovl4, the key enzymes mediating long-chain fatty acid elongation[23-24].

Consistent transcriptomic profiling of human DR central retinas shows widespread downregulation of genes involved in *de novo* fatty acid synthesis (PLA2G4A, HADHA), cholesterol metabolism, and glycerophospholipid biosynthesis, with only sphingomyelin phosphodiesterase 1 (SMPD1) and lysophosphatidylcholine acyltramsferase 3 (LPCAT3) upregulated. Collectively, these data demonstrate severe suppression of both systemic and retinal fatty acid synthesis and elongation pathways in the diabetics[22]. The functional significance of these alterations is underscored by genetic studies showing that neural retina-specific deletion of the rate-limiting enzyme in mice causes progressive retinal neurodegeneration and irreversible vision loss, establishing a causal link between impaired fatty acid metabolism homeostasis and retinal dysfunction[21].

Lipid Peroxidation Lipid peroxidation is the critical intersection of lipid metabolic abnormalities and oxidative stress, forming the central pathological axis that orchestrating the entire DR retinal injury cascade. Retinal photoreceptor outer segments are uniquely enriched in highly oxidizable polyunsaturated fatty acids, rendering them exquisitely vulnerable to reactive oxygen species (ROS)-mediated oxidative damage[25].

In the diabetic retina, aberrant cholesterol and fatty acid metabolism causes pathological lipid deposition, excessive ROS generation, and impaired antioxidant defenses. These synergistic pathological events initiate and propagate lipid peroxidation, leading to accumulation of bioactive products, most notably 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA). These reactive aldehydes exert pleiotropic detrimental effects: directly covalently modify and inactivating proteins, inducing DNA damage and disrupting cell membrane integrity. Furthermore, they act as damage-associated molecular patterns that activate resident innate immune cells (predominantly microglia and Müller cells), initiating a self-amplifying chronic inflammatory response and further stimulating ROS production. This establishes a feedforward vicious cycle of lipid metabolic dysregulation, lipid peroxidation, oxidative stress, and inflammatory activation, perpetuating retinal damage and drives the inexorable progression of DR[11,26-27].

SYNERGISTIC PATHOGENIC MECHANISMS OF OXIDATIVE STRESS AND INFLAMMATION IN DR

Chronic hyperglycemia triggers profound metabolic reprogramming in the retina, characterized by impaired glycolysis and pentose phosphate pathway flux, excessive activation of the polyol pathway, and dysregulation of multiple pathogenic signaling cascades. These include the accumulation of advanced glycation end products and aberrant activation of protein kinase C (PKC) isoforms. All of perturbations converge to induce robust oxidative stress and chronic low-grade inflammation[7]. Crucially, oxidative stress and inflammation are not isolated pathological events but mutually reinforcing processes with extensive bidirectional crosstalk forming a self-perpetuating feedforward pathological loop that amplifies retinal damage and drives relentless progression of DR[28-29].

Mechanisms of Oxidative Stress in DR The retina is exquisitely sensitive to oxidative stress due to two inherent properties: chronic exposure to visible and ultraviolet light that continuously generates ROS *via* photochemical reactions, and the exceptionally high content of oxidizable polyunsaturated fatty acids in daily renewing photoreceptor outer segments[30].

In diabetic, hyperglycemia triggers excessive ROS production through two predominant pathways, overwhelming the retinal antioxidant defense system and disrupting redox homeostasis[31]. First, increased mitochondrial tricatboxylic acid cycle flux causes electron leakage and excessive mitochondrial ROS generation. It also damages mitochondrial DNA (mtDNA) and impairs electron transport chain function, creating a self-amplifying loop of mitochondrial dysfunction and further ROS overproduction[32]. Second, hyperglycemia elevates intracellular diacylglycerol levels, activating PKC isoforms and specifically upregulating nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 2 to produce robust cytoplasmic ROS[33].

Accumulated ROS exert pleiotropic detrimental effects *via* three major mechanisms. First, direct oxidation of cellular macromolecules including proteins, lipids and nucleic acids, causing irreversible structural damage and apoptosis[34]. Second, induction of mitochondrial outer membrane permeabilization and cytochrome C release, activating the caspase-3-dependent apoptotic cascade in retinal neurons and vascular endothelial cells, with emerging evidence implicating lipid peroxidation drived ferroptosis in retinal cell loss[35]. Third, activation of redox-sensitive transcription factors, most notably hypoxia-inducible factor-1α (HIF-1α), which upregulates vascular endothelial growth factor (VEGF) and pro-inflammatory cytokines to drive vascular hyperpermeability, pathological angiogenesis and neuroinflammation[36]. Concomitant with excessive ROS generation, the endogenous antioxidant defense system is severely compromised in DR. Glutathione peroxidase 4 (GPX4), the only mammalian enzyme that reduces lipid hydroperoxides within cell membranes, is functionally impaired due to NADPH depletion, leading to unrestrained lipid peroxidation and ferroptosis[37]. The nuclear factor erythroid 2-related factor 2/Kelch-like ECH-associated protein 1 (Nrf2/Keap1) pathway, the central regulator of cellular antioxidant responses, is dysregulated: enhanced Nrf2-Keap1 interaction impairs Nrf2 nuclear translocation and blunts induction of antioxidant response element-driven detoxification genes, despite unaltered total Nrf2 protein

levels[38-39]. Additionally, key redox regulators including thioredoxin family member Srxn1 and metabolic sensor AMP-activated protein kinase are functionally impaired. Pharmacological AMP-activated protein kinase activation with metformin confers robust antioxidant effects in DR by upregulating superoxide dismutase 2 and restoring redox balance[40-41].

Mechanisms of Chronic Inflammatory Responses in DR Genome-wide association studies have consistently identified inflammation-related genes as major contributors to DR genetic susceptibility, establishing chronic low-grade sterile inflammation as a fundamental pathological hallmark underlying all disease stages[42-43]. Mechanistically, oxidative stress acts as the primary upstream trigger that initiates and sustains retinal inflammation: excess ROS potently induce pro-inflammatory mediator secretion and drive inflammatory cascade amplification, independent of their direct cytotoxic effects[44]. The inflammatory phenotype in DR is defined by two core features: pathological activation of resident innate immune cells and persistent dysregulation of conserved pro-inflammatory signaling networks[45-46].

Abnormal activation of innate immune cells Microglia, the resident innate immune cells of the retina, continuously survey the microenvironment *via* dynamic processes and are rapidly and persistently activated by high glucose[47]. In early DR, microglia predominantly exhibit a neuroprotective anti-inflammatory M2-like phenotype; with disease progression, they switch to a pro-inflammatory M1 phenotype, releasing robust amounts of tumor necrosis factor-α, interleukin (IL)-1β, IL-6, ROS and inducible nitric oxide synthase. These mediators further reinforce the pro-inflammatory phenotype, exacerbating retinal neuronal apoptosis and synaptic dysfunction[48]. Activated microglia also secrete matrix metalloproteinases that degrade extracellular matrix and tight junction proteins, compromising BRB integrity, and release angiogenic factors [VEGF, IL-6, matrix metalloproteinase (MMP)-2 and MMP-9] to drive pathological neovascularization[49-50]. Microglia-derived galectin-3 inhibits Notch signaling by binding Jagged1, promoting endothelial cell proliferation and choroidal neovascularization. Furthermore, microglial activation depends on ATP supplied by adjacent Müller cells, and macroglia-microglia crosstalk constitutes a critical step in innate immune response amplification[51]. Monocytes/macrophages represent another major class of effector cells mediating retinal inflammatory injury. Monocytes/macrophages represent another major effector cell population mediating retinal inflammatory injury. In DR, peripheral monocytes infiltrate the retina in response to damage-associated molecular patterns, complement activation and chemokine gradients, further amplifying local inflammation[46,52]. Clinical and preclinical studies have demonstrated significant peroxisome proliferator-activated receptor α (PPARα) downregulation in monocytes from DR patients and animal models, accompanied by aberrant cyclic guanosine monophosphate—adenosine monophosphate synthase (cGAS)—stimulator of interferon genes (STING) pathway hyperactivation, which drives abnormal monocyte activation, leukocyte adhesion, BRB breakdown, and vascular leakage.

Sustained activation of core proinflammatory signaling pathways The nuclear factor-κB (NF-κB) pathway functions as the central integrative hub transducing hyperglycemic stress into pro-inflammatory and pro-apoptotic signals in DR. ROS directly activate NF-κB as early as the preclinical stage, with its activity progressively increasing in parallel with pericyte and endothelial cell apoptosis[53]. In retinal pericytes, sustained NF-κB activation transcriptionally upregulates MMP-9, which aberrantly accumulates in mitochondria and cleaves connexin 43, disrupting mitochondrial membrane integrity, promoting cytochrome C release and establishing a feedforward apoptotic signaling loop[54]. Additionally, NF-κB activation induces nitrosative stress, creating a self-reinforcing positive feedback loop that maintains its own persistent activation, leading to robust pro-inflammatory cytokine upregulation, increased vascular permeability and diabetic macular edema[55].

The cGAS-STING pathway has emerged as the master regulator of sterile inflammation in DR, bridging mitochondrial dysfunction, oxidative stress, and inflammatory activation. Originally identified as a microbial DNA sensor, cGAS-STING is now established as a key mediator of sterile inflammation triggered by damaged self-DNA. Upon detecting cytoplasmic DNA, cGAS produces 2'3'-cGAMP, which activates STING on the endoplasmic reticulum. Activated STING recruits and phosphorylates TANK-binding kinase 1, which in turn phosphorylates interferon regulatory factor 3 to induce type I interferon production and activates the inhibitor of κB kinase complex to trigger NF-κB-dependent gene expression[56-57]. In the diabetic retina, high glucose-induced mitochondrial calcium overload opens the mitochondrial permeability transition pore, causing mtDNA leakage into the cytoplasm and subsequent cGAS activation[56]. Widespread mitochondrial dysfunction in Müller cells and retinal microvascular endothelial cells further promotes mtDNA release and sustains chronic cGAS-STING signaling, driving endothelial cell senescence, leukocyte recruitment, BRB breakdown, vascular leakage and pathological angiogenesis[37,58]. Notably, under hyperlipidemic conditions, the inositol-requiring enzyme 1α–X-box binding protein 1 endoplasmic reticulum stress pathway also activates STING, adding an additional layer of crosstalk between metabolic dysfunction and inflammation[59].

Other important pro-inflammatory pathways in DR include the high mobility group box 1 (HMGB1)-receptor for advanced glycation end products axis and the cyclooxygenase-2/prostaglandin E2/prostaglandin E receptor 2 cascade. HMGB1, released from damaged retinal cells, acts as a damage-associated molecular pattern to activate NF-κB *via* receptor for advanced glycation end products and Toll-like receptors, promoting inflammation, endothelial apoptosis, and BRB disruption; the deacetylase sirtuin 1 negatively regulates HMGB1 activity, and resveratrol attenuates retinal inflammation by inhibiting HMGB1 signaling. Under hypoxic conditions, the cyclooxygenase-2/prostaglandin E2/prostaglandin E receptor 2 axis is the predominant pathway driving VEGF A and IL-6 expression in microglia, mediating hypoxia-induced inflammation and neovascularization[60].

Reciprocal Regulatory Loop Between Oxidative Stress and Inflammation As highlighted throughout this chapter, oxidative stress and inflammation engage in extensive bidirectional crosstalk, forming a self-perpetuating feedforward loop that constitutes the central pathogenic axis of DR. Oxidative stress acts as the primary upstream trigger, activating NF-κB and cGAS-STING pathways to induce pro-inflammatory cytokine expression and innate immune cell activation. Conversely, activated microglia and infiltrating macrophages generate large quantities of ROS *via* upregulated Nox activity while simultaneously suppressing the Nrf2-mediated antioxidant defense system, creating an imbalance between ROS production and scavenging that further amplifies oxidative damage[61]. This reciprocal amplification loop underpins all stages of DR, driving the transition from early subclinical neurovascular dysfunction to advanced vision-threatening proliferative retinopathy.

PPARs AS THERAPEUTIC TARGETS FOR DR

PPARs are ligand-activated nuclear transcription factors belonging to the steroid hormone receptor superfamily. Upon binding specific ligands, PPARs modulate their transcriptional activity and regulate downstream target gene expression, enabling cellular responses to hormones, vitamins, and lipid metabolites, and participating in diverse physiological and pathological processes[62]. The PPAR subfamily comprises three isoforms encoded by distinct genes: PPARα, peroxisome proliferator-activated receptor β/δ (PPARβ/δ) and peroxisome proliferator-activated receptor γ (PPARγ)[63-64]. Despite high structural homology and shared DNA cis-acting element recognition, they differ markedly in tissue distribution, ligand specificity, and physiological functions. Specifically, PPARα primarily maintains systemic energy homeostasis *via* regulating lipid metabolism, glucose homeostasis, and insulin sensitivity[65]. PPARβ/δ predominantly regulates cerebral lipid metabolism and myelination. PPARγ controls lipid and glucose homeostasis, mitochondrial biogenesis, and inflammatory responses, with predominant expression in adipose and colon tissues, and detectable levels in pancreatic β cells, macrophages, myocardium, and skeletal muscle. At the molecular level, PPARα governs triglyceride catabolism and lipoprotein lipase expression, while PPARγ upregulates key enzymes mediating fatty acid transport into mitochondria and peroxisomes for oxidation[62].

PPARα PPARα is ubiquitously expressed in the retina, localizing to the RPE, outer nuclear layer, inner nuclear layer, and ganglion cell layer. It acts as a pivotal transcriptional regulator of retinal lipid metabolism, neuronal function, and vascular homeostasis[66]. Consistent downregulation of PPARα in both type 1 and type 2 diabetic retinas strongly implicates its aberrant expression in DR pathogenesis and progression[67].

PPARα confers robust retinal protection through three interconnected core mechanisms. First, metabolic-inflammatory phenotype modulation: PPARα transcriptionally regulates monocyte/macrophage metabolic reprogramming and activation. In the oxygen-induced retinopathy model, PPARα overexpression attenuates mitochondrial damage and cytoplasmic mitochondrial DNA release, thereby inhibiting cGAS-STING signaling and retinal myeloid cell activation, and suppressing monocyte activation and leukocyte adhesion. Conversely, PPARα genetic ablation impairs monocyte mitochondrial function, drives aberrant glycolytic reprogramming, and triggers cGAS-STING activation in retinal myeloid cells and glial reactivity, all contributing to DR progression[68-69].

Second, vascular homeostasis maintenance: PPARα preserves retinal vessel structural and functional integrity by inhibiting HIF-1α pathway activation, reducing vascular leakage, pathological neovascularization, and leukocyte adhesion. Third, oxidative stress and inflammatory damage inhibition: The prototypical PPARα agonist fenofibrate exerts DR-protective effects *via* a PPARα-dependent transcriptional program. It downregulates retinal pro-inflammatory and pro-angiogenic factors and selectively modulates lipopolysaccharide-induced NF-κB p65 phosphorylation and pro-inflammatory cytokine production in microglia[70]. Concurrently, fenofibrate mitigates oxidative stress by downregulating miR-21, inhibiting NADPH oxidase activity, increasing superoxide dismutase activity, reducing ROS generation, and suppressing thioredoxin-interacting protein expression, while also attenuating Wnt/β-catenin-mediated retinal damage[6].

Mechanistically, fenofibrate activates the PPARα/peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α) signaling axis, upregulates mitochondrial outer membrane translocase 20, improves mitochondrial function, and exerts anti-inflammatory and anti-apoptotic effects on

retinal neurons and endothelial cells[71-72]. In streptozotocin-induced diabetic rats, fenofibrate significantly reduces retinal leukostasis and albumin leakage, reverses electroretinogram functional deficits, and prevents retinal vascular dysfunction and neurodegeneration[73]. Now, the long-term sustained release microspheres of fenofibrate constructed by high molecular weight poly(lactic-co-glycolic acid) as the carrier can achieve the long-term controlled release of drug in the eye. In streptozotocin-induced DR rat model, the microspheres could effectively activate PPARα/PGC-1α signaling pathway, improve mitochondrial function, play an anti-inflammatory and neuron-protective role, and significantly reduce retinal leukostasis and albumin leakage, and reverse the damage of electroretinogram function. It can effectively prevent retinal vascular dysfunction and neurodegeneration, and provide a feasible clinical transformation scheme for the long-term treatment of DR[74].

Collectively, PPARα is indispensable for maintaining retinal vascular development and integrity, perfusion, neurovascular coupling, BRB integrity, and endothelial metabolic homeostasis. As a master transcription factor linking lipid metabolism and inflammation, PPARα deficiency causes systemic dyslipidemia and monocyte mitochondrial dysfunction, thereby exacerbating DR pathological changes[71,73].

PPARγ PPARγ is a core nuclear receptor governing the entire pathological progression of DR. Pharmacological activation of PPARγ significantly reduces DR risk and exerts bidirectional lipid homeostasis regulation by suppressing *de novo* cholesterol synthesis and enhancing lipid catabolism[75]. A high-glucose milieu upregulates both mRNA and protein levels of PPARγ1 and PPARγ2 isoforms in bovine retinal endothelial cells, with consistent elevation observed in diabetic rat retinas, indicating sophisticated dynamic transcriptional and post-translational regulation of PPARγ during DR pathogenesis.

Upon ligand binding and nuclear translocation, PPARγ-ligand complexes directly interact with pro-inflammatory transcription factors, abrogating their DNA-binding capacity and repressing downstream pro-inflammatory gene transcription to elicit robust anti-inflammatory effects. Within the retinal innate immune system, PPARγ modulates monocyte/macrophage activation phenotypes and preferentially drives macrophage polarization toward the anti-inflammatory M2 phenotype, establishing its pivotal role in retinal innate immune homeostasis[76-77].

Mononuclear phagocytes (MPs), comprising resident microglia and infiltrating monocyte-derived macrophages, are the principal cellular drivers of chronic retinal inflammation and pathological vascular remodeling in DR. Lipid-laden MPs exhibit dysregulated metabolism, phagocytosis, and autophagic flux, releasing excessive ROS and pro-inflammatory mediators to cause progressive retinal damage. Notably, PPARγ activation effectively abrogates lipid-laden MP-mediated retinal vascular degeneration[78-79].

In DR rat retinas, capsaicin suppresses PPARγ signaling by promoting its phosphorylation and ubiquitin-mediated proteasomal degradation, concurrently activates transient receptor potential vanilloid 1 and modulates the PPARγ–Poldip2–Nox4 axis. This cascade inhibits ROS-induced overexpression of vascular cell adhesion molecule-1, HIF-1α and VEGF under hyperglycemic conditions, thereby attenuating retinal vascular leakage and delaying DR progression[80].

PPARγ also functions as a central regulator of mitochondrial metabolic adaptation. Its activation upregulates key mitochondrial biogenesis transcription factors, promoting mitochondrial biogenesis, enhancing cellular oxygen consumption and mitochondrial membrane potential, strengthening antioxidant defenses and normalizing autophagic flux[81-82]. As a critical hub integrating glucose and mitochondrial lipid metabolism *via* AMP-activated protein kinase signaling, PPARγ upregulation markedly ameliorates multiple DR pathological hallmarks[79,83].

Finally, PPARγ mediates retinal neuroprotection. Microglial triggering receptor expressed on myeloid cells 2 upregulates scavenger receptor CD36 *via* PPARγ activation, modulating microglial chemotaxis, phagocytosis, survival, and proliferation, and attenuating photoreceptor degeneration[84]. The prototypical PPARγ agonist pioglitazone not only improves systemic insulin sensitivity and lipid metabolism but also protects retinal ganglion cells against ischemic injury, expanding its neuroprotective network through functional crosstalk with low-density lipoprotein receptor-related protein 1[85].

DISCUSSION

This review systematically delineates the synergistic pathogenic network of abnormal lipid metabolism, oxidative stress, and chronic inflammation in DR, focuses on dissecting the regulatory roles of PPARs as central transcriptional factors linking these three pathological processes.

Accumulating evidence indicates that DR is not merely a vascular disorder but rather a neurovascular degenerative disease involving multiple cell types and signaling pathways, with dysregulated lipid metabolism as the upstream initiating factor and the self-amplifying vicious cycle of oxidative stress and inflammation as the core driving force. Among PPAR isoforms, PPARα and PPARγ exert robust retinal protective effects through multiple pathways, including regulating monocyte/macrophage metabolic reprogramming, maintaining vascular homeostasis, improving mitochondrial function, and inhibiting oxidative stress injury, making them highly

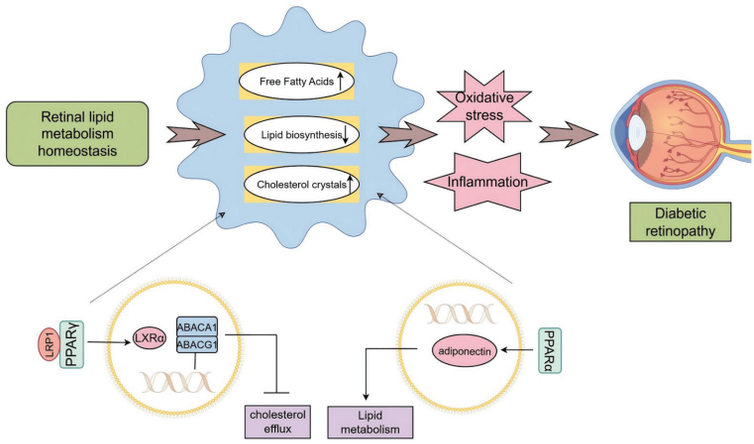


Figure 1 Protective role of PPARs in oxidative stress and immune processes induced by lipid metabolism disorder in DR LRP1: Low-density lipoprotein receptor-related protein 1; PPARγ: Peroxisome proliferator-activated receptor γ; LXRα: Liver X receptor α; ABCA1: ATP-binding cassette transporter A1; ABCG1: ATP-binding cassette transporter G1; PPARα: Peroxisome proliferator-activated receptor α; DR: Diabetic retinopathy.

promising therapeutic targets for DR. However, traditional PPAR agonists face clinical application bottlenecks such as poor ocular bioavailability and significant systemic side effects. The emergence of novel delivery systems, represented by biomimetic cell membrane-modified nanoparticles and poly(lactic-co-glycolic acid) long-acting sustained-release microspheres, provides feasible translational strategies for the precise and long-term ocular delivery of PPAR-targeted drugs.

Despite remarkable advances in basic research on PPAR-targeted therapy for DR, several critical challenges remain. First, the specific roles and underlying mechanisms of PPARβ/δ in DR pathogenesis have not been fully elucidated. Second, existing PPAR agonists lack sufficient subtype selectivity, which easily causes adverse effects associated with cross-activation. Third, the long-term safety and large-scale manufacturing processes of nanomedicines still require further optimization. Future studies should focus on developing highly selective PPAR subtype agonists, constructing multifunctional targeted nanodelivery systems, and conducting well-designed multicenter clinical trials to validate their clinical efficacy, thereby providing novel theoretical basis and therapeutic strategies for the precise prevention and treatment of DR (Figure 1).

ACKNOWLEDGEMENTS

Authors' Contributions: Zhang YG: conceptualization; visualization; validation; writing-original draft; Zhang MJ: visualization; validation; writing-review & editing; Sun M: conceptualization; writing-original draft; Xu J: conceptualization; validation; Xie LK: writing-review & editing; supervision and funding; Hao XF: writing-review & editing; supervision and funding. All authors read and approved the final manuscript.

AI-Generated Content Disclosure: No generative AI-generated content was used in any part of this manuscript.

Foundations: Supported by the Central High-level Traditional Chinese Medicine Hospital Project, Eye Hospital of China Academy of Chinese Medical Sciences (No.GSP5-96; No.GSP5-83; No.GSP4-02-3); the National Natural Science Foundation of China (No.82474582).

Conflicts of Interest: Zhang YG, None; **Zhang MJ,** None; **Sun M,** None; **Xu J,** None; **Xie LK,** None; **Hao XF,** None.

REFERENCES

1 Zhao LJ, Yuan JM, Yang Q, *et al*. Diabetes and its complications: molecular mechanisms, prevention and treatment. *Sig Transduct Target Ther* 2026;11(1):22.

2 Li YW, Liu YF, Liu SW, *et al*. Diabetic vascular diseases: molecular mechanisms and therapeutic strategies. *Sig Transduct Target Ther* 2023;8(1):152.

3 Teo ZL, Tham YC, Yu M, *et al*. Global prevalence of diabetic retinopathy and projection of burden through 2045: systematic review and meta-analysis. *Ophthalmology* 2021;128(11):1580-1591.

4 Sivaprasad S, Wong TY, Gardner TW, *et al*. Diabetic retinal disease. *Nat Rev Dis Primers* 2025;11(1):62.

5 Tan TE, Wong TY. Diabetic retinopathy: looking forward to 2030. *Front Endocrinol (Lausanne)* 2023;13:1077669.

6 Joharapurkar A, Patel V, Kshirsagar S, *et al*. Effect of dual PPAR-α/γ agonist saroglitazar on diabetic retinopathy and oxygen-induced retinopathy. *Eur J Pharmacol* 2021;899:174032.

7 Parashar R, Suresh PK. Emerging liposomal therapies for diabetic retinopathy: a review of novel targeting approaches and advances in retinal health outcomes. *Drug Deliv* 2025;32(1):2509973.

8 Sun YX, Zhang ZR, Chen ZJ, *et al*. Novel high-resolution lipidomes could serve as new biomarkers for diabetic retinopathy: a bidirectional and mediated Mendelian randomization study. *J Cell Mol Med* 2025;29(11):e70614.

9 Sharma A, Kizy S, Singh NK. Understanding the molecular basis of pathological retinal angiogenesis: roles of lipids, non-coding RNAs, and cellular crosstalk. *Invest Ophthalmol Vis Sci* 2026;67(3):33.

10 Jenkins AJ, Grant MB, Busik JV. Lipids, hyperreflective crystalline deposits and diabetic retinopathy: potential systemic and retinal-specific effect of lipid-lowering therapies. *Diabetologia* 2022;65(4):587-603.

11 Ana RD, Gliszczyńska A, Sanchez-Lopez E, *et al*. Precision medicines for retinal lipid metabolism-related pathologies. *J Pers Med* 2023;13(4):635.

12 Ohguro H, Watanabe M, Hikage F, *et al*. Fatty acid-binding protein 4-mediated regulation is pivotally involved in retinal pathophysiology: a review. *Int J Mol Sci* 2024;25(14):7717.

13 Zhang X, Alhasani RH, Zhou XZ, *et al*. Oxysterols and retinal degeneration. *Br J Pharmacol* 2021;178(16):3205-3219.

14 Ramachandra Rao S, Fliesler SJ. Cholesterol homeostasis in the vertebrate retina: biology and pathobiology. *J Lipid Res* 2021;62:100057.

15 Yang JL, Chen YH, Zou TD, *et al*. Cholesterol homeostasis regulated by ABCA1 is critical for retinal ganglion cell survival. *Sci China Life Sci* 2023;66(2):211-225.

16 Hammer SS, Dorweiler TF, McFarland D, *et al*. Cholesterol crystal formation is a unifying pathogenic mechanism in the development of diabetic retinopathy. *Diabetologia* 2023;66(9):1705-1718.

17 Eid S, Sas KM, Abcouwer SF, *et al*. New insights into the mechanisms of diabetic complications: role of lipids and lipid metabolism. *Diabetologia* 2019;62(9):1539-1549.

18 Vieira CP, Fortmann SD, Hossain M, *et al*. Selective LXR agonist DMHCA corrects retinal and bone marrow dysfunction in type 2 diabetes. *JCI Insight* 2020;5(13):e137230.

19 Swinkels D, Baes M. The essential role of docosahexaenoic acid and its derivatives for retinal integrity. *Pharmacol Ther* 2023;247:108440.

20 Zou R, Cai JR, Chen TY, *et al*. High-fat diet alters retinal lipid composition and gene expression networks in mice. *BMC Biol* 2025;23(1):103.

21 Wang YX, Becker S, Finkelstein S, *et al*. Acyl-CoA synthetase 6 controls rod photoreceptor function and survival by shaping the phospholipid composition of retinal membranes. *Commun Biol* 2024;7(1):1027.

22 Fort PE, Rajendiran TM, Soni T, *et al*. Diminished retinal complex lipid synthesis and impaired fatty acid β-oxidation associated with human diabetic retinopathy. *JCI Insight* 2021;6(19):e152109.

23 Tikhonenko M, Lydic TA, Wang Y, *et al*. Remodeling of retinal Fatty acids in an animal model of diabetes: a decrease in long-chain polyunsaturated fatty acids is associated with a decrease in fatty acid elongases Elovl2 and Elovl4. *Diabetes* 2010;59(1):219-227.

24 Gorusupudi A, Rallabandi R, Li BX, *et al*. Retinal bioavailability and functional effects of a synthetic very-long-chain polyunsaturated fatty acid in mice. *Proc Natl Acad Sci U S A* 2021;118(6):e2017739118.

25 Kuroha S, Katada Y, Isobe Y, *et al*. Long chain acyl-CoA synthetase 6 facilitates the local distribution of di-docosahexaenoic acid- and ultra-long-chain-PUFA-containing phospholipids in the retina to support normal visual function in mice. *FASEB J* 2023;37(9):e23151.

26 Kumar B, Kowluru A, Kowluru RA. Lipotoxicity augments glucotoxicity-induced mitochondrial damage in the development of diabetic retinopathy. *Invest Ophthalmol Vis Sci* 2015;56(5):2985-2992.

27 Xu XY, Pang Y, Fan XQ. Mitochondria in oxidative stress, inflammation and aging: from mechanisms to therapeutic advances. *Sig Transduct Target Ther* 2025;10(1):190.

28 Che ST, Ma Y, Fu JL, *et al*. Oxidative stress in diabetic retinopathy: metabolic triggers, molecular pathways and emerging antioxidant therapies. *Int J Biol Macromol* 2026;344(Pt 2):150272.

29 Parveen A, Kim JH, Oh BG, *et al*. Phytochemicals: target-based therapeutic strategies for diabetic retinopathy. *Molecules* 2018;23(7):1519.

30 Dohl J, Burns G, Singh M. The intersection of mitochondria, lipids, and ferroptosis: a new avenue for dry age-related macular degeneration. *Apoptosis* 2025;30(11-12):2526-2546.

31 Brooks CD, Kodati B, Stankowska DL, *et al*. Role of mitophagy in ocular neurodegeneration. *Front Neurosci* 2023;17:1299552.

32 Hu XJ, Lv J, Zhao YY, *et al*. Important regulatory role of mitophagy in diabetic microvascular complications. *J Transl Med* 2025;23(1):269.

33 Kowluru RA. Diabetic retinopathy and NADPH oxidase-2: a sweet slippery road. *Antioxidants* (*Basel*) 2021;10(5):783.

34 Chang KC, Liu PF, Chang CH, *et al*. The interplay of autophagy and oxidative stress in the pathogenesis and therapy of retinal degenerative diseases. *Cell Biosci* 2022;12(1):1.

35 Malaviya P, Kumar J, Kowluru RA. Role of ferroptosis in mitochondrial damage in diabetic retinopathy. *Free Radic Biol Med* 2024;225:821-832.

36 Ichiyama Y, Sapieha P. Hypoxia-inducible factors link poor glycemic controlto diabetic retinopathy. *Sci Transl Med* 2025;17(796):eadu7718.

37 Liu Q, Liu CQ, Yi WZ, *et al*. Ferroptosis contributes to microvascular dysfunction in diabetic retinopathy. *Am J Pathol* 2024;194(6):1078-1089.

38 Jiménez-Loygorri JI, Benítez-Fernández R, Viedma-Poyatos Á, *et al*. Mitophagy in the retina: viewing mitochondrial homeostasis through a new lens. *Prog Retin Eye Res* 2023;96:101205.

39 Zhu F, Shao J, Tian YL, *et al*. Sulfiredoxin-1 protects retinal ganglion cells from high glucose-induced oxidative stress and inflammatory injury by potentiating Nrf2 signaling *via* the Akt/GSK-3β pathway. *Int Immunopharmacol* 2021;101(Pt B):108221.

40 Park Y, Jeong Y, Son S, *et al*. AMPK-induced mitochondrial biogenesis decelerates retinal pigment epithelial cell degeneration under nutrient starvation. *BMB Rep* 2023;56(2):84-89.

41 Li LH, Chen J, Zhou Y, *et al*. Artesunate alleviates diabetic retinopathy by activating autophagy *via* the regulation of AMPK/SIRT1 pathway. *Arch Physiol Biochem* 2023;129(4):943-950.

42 Deng BX, Nnebe C, Prakhar P, *et al*. New insights into diabetes-induced cell-type-specific responses in the neural retina *via* single-cell transcriptomics: a report on research supported by pathway to stop diabetes. *Diabetes* 2025;74(10):1720-1726.

43 Niu T, Fang JW, Shi X, *et al*. Pathogenesis study based on high-throughput single-cell sequencing analysis reveals novel transcriptional landscape and heterogeneity of retinal cells in type 2 diabetic mice. *Diabetes* 2021;70(5):1185-1197.

44 Yang L, Yao Y, Zheng WD, *et al*. Nitric oxide mediates negative feedback on the TXNIP/NLRP3 inflammasome pathway to prevent retinal neurovascular unit dysfunction in early diabetic retinopathy. *Free Radic Biol Med* 2025;233:279-291.

45 Pan WW, Lin F, Fort PE. The innate immune system in diabetic retinopathy. *Prog Retin Eye Res* 2021;84:100940.

46 Sun YM, Li F, Liu YF, *et al*. Targeting inflammasomes and pyroptosis in retinal diseases-molecular mechanisms and future perspectives. *Prog Retin Eye Res* 2024;101:101263.

47 Hu AY, Schmidt MHH, Heinig N. Microglia in retinal angiogenesis and diabetic retinopathy. *Angiogenesis* 2024;27(3):311-331.

48 Cai LW, Xia MX, Zhang F. Redox regulation of immunometabolism in microglia underpinning diabetic retinopathy. *Antioxidants* (*Basel*) 2024;13(4):423.

49 Bai YY, Wang XR, Qi F, *et al*. Mechanisms of action of retinal microglia in diabetic retinopathy (Review). *Int J Mol Med* 2025;56(6):202.

50 Sun WJ, An XD, Zhang YH, *et al*. The ideal treatment timing for diabetic retinopathy: the molecular pathological mechanisms underlying early-stage diabetic retinopathy are a matter of concern. *Front Endocrinol (Lausanne)* 2023;14:1270145.

51 Li ZL, Xiong Q, Li Q, *et al*. Parthenolide ameliorates diabetic retinopathy by suppressing microglia-induced Müller cell gliosis and inflammation *via* the NF-κB signalling. *Int Immunopharmacol* 2025;151:114219.

52 Zhang Y, Zhou AY. Macrophage activation contributes to diabetic retinopathy. *J Mol Med* (*Berl*) 2024;102(5):585-597.

53 Yu ZY, Lu B, Sheng YC, *et al*. Andrographolide ameliorates diabetic retinopathy by inhibiting retinal angiogenesis and inflammation. *Biochim Biophys Acta* 2015;1850(4):824-831.

54 Dharmarajan S, Carrillo C, Qi ZH, *et al*. Retinal inflammation in murine models of type 1 and type 2 diabetes with diabetic retinopathy. *Diabetologia* 2023;66(11):2170-2185.

55 Ciorba AL, Saber S, Abdelhamid AM, *et al*. Diabetic retinopathy in focus: update on treatment advances, pharmaceutical approaches, and new technologies. *Eur J Pharm Sci* 2025;214:107307.

56 Wang XS, Feng ZH, Sun S, *et al*. cGAS-STING-driven inflammaging cascade in aging-related retinal diseases: from pathological mechanism to therapeutic potentials. *Ageing Res Rev* 2026;114:102983.

57 Wu XD, Yu NJ, Ye ZF, *et al*. Inhibition of cGAS-STING pathway alleviates neuroinflammation-induced retinal ganglion cell death after ischemia/reperfusion injury. *Cell Death Dis* 2023;14(9):615.

58 Hu B, Ma JX, Duerfeldt AS. The cGAS–STING pathway in diabetic retinopathy and age-related macular degeneration. *Future Med Chem* 2023;15(8):717-729.

59 Wen ZY, He XM, Wang J, *et al*. Hyperlipidemia induces proinflammatory responses by activating STING pathway through IRE1α-XBP1 in retinal endothelial cells. *J Nutr Biochem* 2023;112:109213.

60 Kishishita S, Usui-Ouchi A, Ouchi Y, *et al*. Proliferative diabetic retinopathy microenvironment drives microglial polarization and promotes angiogenesis and fibrosis *via* cyclooxygenase-2/prostaglandin E2 signaling. *Int J Mol Sci* 2024;25(20):11307.

61 Pan WW, Wubben TJ, Besirli CG. Photoreceptor metabolic reprogramming: current understanding and therapeutic implications. *Commun Biol* 2021;4(1):245.

62 Titus C, Hoque MT, Bendayan R. PPAR agonists for the treatment of neuroinflammatory diseases. *Trends Pharmacol Sci* 2024;45(1):9-23.

63 Qiu YY, Zhang J, Zeng FY, *et al*. Roles of the peroxisome proliferator-activated receptors (PPARs) in the pathogenesis of nonalcoholic fatty liver disease (NAFLD). *Pharmacol Res* 2023;192:106786.

64 Wang GF, Yan Y, Sun Q, *et al*. Distinct roles of PPARs in atherosclerosis. *Arterioscler Thromb Vasc Biol* 2026;46(1):68-84.

65 Cheng ZQ, Zhan HH, Yuan H, *et al*. Boeravinone C ameliorates lipid accumulation and inflammation in diabetic kidney disease by activating PPARα signaling. *J Ethnopharmacol* 2025;342:119398.

66 Sun TB, Huang KF, Niu KC, *et al*. Hyperbaric oxygen therapy suppresses hypoxia and reoxygenation injury to retinal pigment epithelial cells through activating peroxisome proliferator activator receptor-alpha signalling. *J Cell Mol Med* 2023;27(20):3189-3201.

67 Chen Y, Hu Y, Lin MK, *et al*. Therapeutic effects of PPARα agonists on diabetic retinopathy in type 1 diabetes models. *Diabetes* 2013;62(1):261-272.

68 Ma X, Wu WJ, Liang WT, *et al*. Modulation of cGAS-STING signaling by PPARα in a mouse model of ischemia-induced retinopathy. *Proc Natl Acad Sci U S A* 2022;119(48):e2208934119.

69 Yuan T, Dong LJ, Pearsall EA, *et al*. The protective role of microglial PPARα in diabetic retinal neurodegeneration and neurovascular dysfunction. *Cells* 2022;11(23):3869.

70 Pan WW, Wubben TJ, Zacks DN. Promising therapeutic targets for neuroprotection in retinal disease. *Curr Opin Ophthalmol* 2025;36(3):247-252.

71 Xu LM, Cheng R, Zhou KL, *et al*. Peroxisome proliferator-activated receptor α deficiency induces vascular pathologies through endothelial senescence in diabetic retinopathy. *Am J Pathol* 2026;196(4):960-975.

72 Cui Y, Poudel S, Xu N, *et al*. Sustained release of a novel non-fibrate PPARα agonist from microparticles for neuroprotection in murine models of age-related macular degeneration. *J Control Release* 2025;380:910-926.

73 Dong LJ, Cheng R, Ma X, *et al*. Regulation of monocyte activation by PPARα through interaction with the cGAS-STING pathway. *Diabetes* 2023;72(7):958-972.

74 Poudel S, Cui Y, Meng T, *et al*. Long-acting fenofibrate-loaded microparticles for treating retinal disorders. *Int J Pharm* 2026;689:126503.

75 Cao JH, Su T, Chen SL, *et al*. Evaluating lipid-lowering drug targets for full-course diabetic retinopathy. *Br J Ophthalmol* 2025;109(8): 868-874.

76 Zhang JL, Wang Z, Liu JJ, *et al*. Dysregulation of the TNF-α-OTUD3-PPARγ signaling axis exacerbates retinal oxidative stress and inflammation in diabetic retinopathy. *Life Sci* 2025;380:123933.

77 Zuo SM, Wang YX, Bao HJ, *et al*. Lipid synthesis, triggered by PPARγ T166 dephosphorylation, sustains reparative function of macrophages during tissue repair. *Nat Commun* 2024;15(1):7269.

78 Blot G, Karadayi R, Przegralek L, *et al*. Perilipin 2-positive mononuclear phagocytes accumulate in the diabetic retina and promote PPARγ-dependent vasodegeneration. *J Clin Invest* 2023;133(19):e161348.

79 Ying WY, Weng WD, Wang PF, *et al*. N-Lactoyl-Phenylalanine modulates lipid metabolism in microglia/macrophage *via* the AMPK-PGC1α-PPARγ pathway to promote recovery in mice with spinal cord injury. *J Neuroinflammation* 2025;22(1):167.

80 Liu K, Gao X, Hu CY, *et al*. Capsaicin ameliorates diabetic retinopathy by inhibiting poldip2-induced oxidative stress. *Redox Biol* 2022;56:102460.

81 Hu ZW, Pang JH, Liu XL, *et al*. PGC-1α transcriptionally regulated by ChREBP mitigates neuropathic pain through promoting microglial fatty acid oxidation and anti-inflammatory response. *CNS Neurosci Ther* 2026;32(1):e70744.

82 Jamwal S, Blackburn JK, Elsworth JD. PPARγ/PGC1α signaling as a potential therapeutic target for mitochondrial biogenesis in neurodegenerative disorders. *Pharmacol Ther* 2021;219:107705.

83 Feng H, Wang JY, Yu B, *et al*. Peroxisome proliferator-activated receptor-γ coactivator-1α inhibits vascular calcification through sirtuin 3-mediated reduction of mitochondrial oxidative stress. *Antioxid Redox Signal* 2019;31(1):75-91.

84 Zhou WC, He JC, Shen GY, *et al*. TREM2-dependent activation of microglial cell protects photoreceptor cell during retinal degeneration *via* PPARγ and CD36. *Cell Death Dis* 2024;15(8):623.

85 Wei M, Huo YJ, Yuan JC, *et al*. Alpinetin nanoparticles alleviate optic nerve injury induced by acute glaucoma *via* LRP1-PPARγ mediated regulation of microglial lipid metabolism. *Adv Sci* (*Weinh*) 2026;13(5):e13270.