



Beyond glycemia: The influence of systemic inflammation, lipids, and the gut-retina axis in diabetic retinopathy

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Abstract

Diabetic retinopathy is a primary cause of visual impairment in individuals with diabetes and represents a multifaceted process that transcends glucose dysregulation. This review analyzes the interconnected roles of systemic inflammation, lipid metabolism, and the gut-retina axis in retinal vascular and neuronal damage. A systematic search of PubMed and Scopus spanning January 2014 to August 2025, revealed experimental and clinical research associating inflammatory cytokines, lipid dysregulation, and abnormalities in gut microbiota with diabetic retinopathy. Evidence suggests that persistent low-grade inflammation, characterized by elevated levels of interleukin-6, tumor necrosis factor-alpha, and interleukin-1 beta, compromises the blood-retinal barrier and accelerates microvascular degeneration. Alterations in lipid pathways, such as reduced docosahexaenoic acid levels, hinder cholesterol efflux and ceramide buildup, exacerbating oxidative stress and neurovascular impairment. Gut microbial dysbiosis diminishes short-chain fatty acid production and fosters endotoxemia, thereby exacerbating retinal inflammation through systemic immune activation. Novel therapeutic strategies that regulate peroxisome proliferator-activated receptor-alpha and restore the microbiota demonstrate synergistic potential to reduce disease progression. The integration of these systems offers a biological foundation for the prevention and therapy of diabetic retinopathy.

Key Words: Systemic inflammation; Gut-retina axis; Dyslipidemia; Diabetic retinopathy; Metabolic memory

Core Tip: Diabetic retinopathy is now recognized as a systemic condition affected not just by chronic hyperglycemia but also by ongoing inflammation, lipid dysregulation, and abnormalities in the gut flora. These interrelated pathways lead to retinal vascular impairment, neurodegeneration, and disease advancement. Identifying these characteristics provides a comprehensive framework for understanding disease pathophysiology and discovering novel therapeutic targets that extend beyond glycemic control.

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INTRODUCTION

Diabetes mellitus (DM) represents a major contributor to global morbidity and mortality through its broad spectrum of vascular complications, encompassing microvascular damage (retinopathy, nephropathy, neuropathy) and macrovascular involvement (coronary, cerebrovascular, and peripheral arterial disease)[1]. Diabetic retinopathy (DR) continues to be a predominant cause of visual impairment in adults globally[2]. The public health implications of DR have warranted early identification and mechanism-based interventions that surpass mere glucose control.

In the United States, the DR prevalence is reported in nearly 30% of diabetic adults, equivalent to about 4.2 million people. At the same time, globally, the proportion reaches 34.6%, affecting around 93 million people[3]. Data showed that by 2020, the United States alone faced approximately 6 million DR cases[4]. Given the enormous burden of DM, including health expenditures, the urgency of timely screening strategies and innovative therapeutic approaches becomes evident [5]. Traditionally viewed as a microvascular complication[6], DR is now considered a neurovascular disorder[7], with neuronal damage detectable before clinical evidence of microvascular lesions[8]. Its pathogenesis is multifactorial, involving chronic hyperglycemia, retinal neovascularization, chronic inflammation, metabolic dysregulation, and immune alterations[9]. This review explores the interconnections between biological networks beyond glycemic regulation, including systemic inflammation, lipid dysmetabolism, and gut microbial signaling, which collectively affect retinal vascular, neuronal, and immune integrity.

DR is clinically classified into “non-proliferative (NPDR)” and “proliferative (PDR)” stages, with diabetic macular edema being a vision-threatening consequence that may arise at any stage[10,11]. In this clinical context, increasing evidence suggests that DR is a neurovascular condition characterized by the concurrent development of neuronal dysfunction and glial activation alongside microvascular damage. In contrast, PDR is defined by the emergence of fragile and abnormal vessels.

In particular, vascular endothelial growth factor (VEGF) plays a crucial role by driving new blood vessel formation and enhancing vascular permeability[12]. While anti-VEGF agents have improved outcomes, they require frequent intravitreal injections, benefit mainly advanced stages, and yield suboptimal responses in nearly half of patients[13]. Advances in retinal imaging have revealed early neuroretinal dysfunction in diabetes[14], yet no approved treatments currently target these early events. Inflammation has emerged as a crucial driver of DR progression[3]. Suppression of inflammatory pathways can mitigate retinal injury in animal models and approaches[15].

Recent studies indicate a bidirectional interaction between gut bacteria and ocular tissues[16]. Instead of a single pathway, many microbiota-derived mediators, metabolites such as short-chain fatty acids (SCFAs), endotoxins, and extracellular vesicles, have been shown to affect retinal immune modulation, barrier integrity, and metabolic processes [17]. Host and dietary factors dynamically modulate the retinal microenvironment, influencing vulnerability to neurovascular dysfunction in DR[18]. Converging clinical and experimental studies demonstrate that intestinal dysbiosis has altered systemic inflammatory tone and metabolite availability, subsequently affecting retinal glia, endothelial cells, and neurons[19]. Disruptions in SCFAs, barrier integrity, and microbial vesicle transport have surfaced as potential connections between gut signals and retinal immune-metabolic equilibrium in diabetes.

Factors such as diet and probiotics influence gut composition and, consequently, the risk of retinal disease[20]. In diabetes, hyperglycemia, neovascularization, and microvascular injury contribute to ocular complications such as cataract, glaucoma, and DR[21]. Gut dysbiosis has been associated with retinal neurodegeneration, heightened inflammatory signaling, and metabolic dysfunction[22]. Conversely, DR itself can alter gut microbial composition, creating a feedback loop that may worsen disease[23,24]. Together, these findings position inflammation, lipid metabolism, and the gut microbiota as contributors to DR pathophysiology and as promising therapeutic targets. Understanding these mechanisms could enable the development of novel nutritional, microbial, and pharmacological strategies to slow or prevent disease progression.

This review aims to synthesize evidence that systemic and retinal inflammatory processes precede and exacerbate neurovascular injury in DR; delineate how lipid metabolism, including fatty acid remodeling, cholesterol transport/efflux, oxysterol signaling, and sphingolipid reprogramming, has contributed to failure of blood retinal barrier (BRB) and neurodegeneration; and evaluate the gut-retina axis as a mechanistic contributor and potential therapeutic target. We also emphasize translational implications encompassing anti-inflammatory, lipid-targeted, and microbiota-directed approaches.

SYSTEMIC INFLAMMATION IN DR

Inflammation serves as a crucial extra-glycemic factor connecting metabolic stress to retinal microvascular and neuroglial damage. During infections, pathogens are identified through pattern recognition receptors. Among them, Toll-like receptors and the receptor for advanced glycation end products are the most important[3]. These receptors are activated by pathogen-associated molecular patterns[25]. The engagement of Toll-like receptors or cellular stress occurring in sterile conditions leads to activation of the nuclear factor kappa B (NF- κ B) pathway. NF- κ B promotes the transcription of various molecules, such as interleukin (IL)-6, tumor necrosis factor- α (TNF- α), IL-1 β , monocyte chemoattractant protein 1 (MCP-1), and acute-phase proteins, that drive inflammation by recruiting and activating circulating immune cells. Normally, this response is self-limiting, resolved by lipid-derived mediators such as resolvins, lipoxins, and protectins[26]. However, when resolution fails, inflammation becomes chronic, resulting in tissue damage rather than protection[27].

A substantial body of research highlights inflammation as a key mechanism DR[28,29]. Elevated levels of pro-inflammatory mediators, including cytokines and chemokines, have been detected in intraocular compartments, such as the aqueous and vitreous humor, in individuals with DR. Remarkably, signs of glial activation can occur even before clinical manifestations of retinopathy become evident. For example, increased levels of glial fibrillary acidic protein have been found in the aqueous humor, reflecting early activation of Muller glial cells[30]. These cells contribute to inflammatory processes by releasing adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1) and MCP-2, which drive leukocyte adhesion and accumulation (leukostasis) in DR[31].

Within the retina, microglia have transitioned to a pro-inflammatory phenotype (classically termed “M1-like”), enhancing NF- κ B signaling and interacting with Muller glia to upregulate ICAM-1/vascular cell adhesion molecule 1, thereby facilitating leukostasis[31]. The disassembly of tight junctions in the inner BRB occurs through expression of VEGF, angiopoietin-2, and cytokine-mediated phosphorylation of occludin and claudin 5[11]. Hypoxia-inducible pathways have also been linked to metabolic stress. In contrast, complement components and damage-associated molecular patterns, such as high mobility group box 1, have exacerbated paracrine damage. These circuits have collectively impacted DR[3].

Cytokines, including IL-1 β , IL-6, IL-8, TNF- α , and MCP-1, are consistently augmented in eyes with NPDR. Interestingly, IL-8 and TNF- α levels have been found to be even higher in NPDR than in PDR[32]. These mediators are secreted not only by microglia and endothelial cells but also by macroglia and neurons, suggesting that inflammation progressively involves multiple retinal cell types[33]. In mouse models, their accumulation has been implicated in early neuronal apoptosis, and certain cytokines also contribute to angiogenesis[34]. At this early stage, glial cells may attempt to counterbalance injury by increasing the secretion of neurotrophic factors such as nerve growth factor, brain-derived neurotrophic factor, neurotrophin 3 and 4, ciliary neurotrophic factor, and glial cell line-derived neurotrophic factor, which are elevated more in NPDR than in PDR[32].

As DR advances to PDR, vitreous levels of cytokines with pro-inflammatory activity, neurotrophins, and angiogenic factors, including VEGF, platelet-derived growth factor, insulin-like growth factor, basic fibroblast growth factor, and hepatocyte growth factor, rise substantially[35]. Soluble cytokine receptors, such as serum IL-2R, are also elevated, representing a natural negative feedback mechanism[36]. Additionally, matrix metalloproteinases, which regulate extracellular matrix remodeling and endothelial cell migration, are upregulated, facilitating pathological angiogenesis[37]. In diabetic macular edema, angiopoietin-2 is markedly elevated alongside inflammatory mediators and VEGF[38]. Levels of VEGF, hepatocyte growth factor, IL-6, and MCP-1 increase with DR severity, and IL-6 correlates with macular thickness[39].

Importantly, vitreous protein elevations in DR reflect genuine intraocular synthesis rather than passive leakage, since total protein levels are similar between NPDR and PDR[32].

Experimental evidence shows that endothelial cells are particularly responsive to inflammatory stimuli. IL-1 β , TNF- α , and interferon gamma induce these cells to secrete chemokines, including MCP-1, and upon activation, express and secrete normal T-cells along with adhesion molecules like ICAM-1 and vascular cell adhesion molecule-1, thereby facilitating leukocyte adhesion to the vascular wall (leukostasis)[40]. Findings from animal models reveal that this leukocyte binds to retinal capillaries merely weeks after the onset of diabetes, preceding detectable microvascular alterations[41]. The cascade that follows involves enhanced vascular permeability, pericyte degeneration, thickening of the basement membrane, and eventual capillary obstruction[42]. The ensuing hypoxic and ischemic environment activates hypoxia-inducible factor-1 mediated pathways in endothelial and glial cells, stimulating the production of VEGF, TNF- α , and IL-6[43]. Moreover, in the ischemic retinal region, chemokines such as MCP-1 recruit macrophages, further amplifying the inflammatory circuit[44].

Cytokines and growth factors jointly regulate angiogenesis in PDR. Blocking inflammation suppresses neovascularization; deletion of MCP-1, ICAM-1, or CD18 markedly reduced aberrant vessel growth in experimental models[45]. Similarly, inhibition of cyclooxygenase 2 lowered VEGF production and attenuated vascular leakage[46]. When secreted by activated immune and retinal cells, high mobility group box 1 contributed to angiogenesis by increasing adhesion molecule expression and triggering VEGF production[47]. Notably, VEGF itself acts as both an angiogenic and an inflammatory mediator, inducing ICAM-1, MCP-1, and IL-8[48].

Animal models of oxygen-induced retinopathy further underscore the link between inflammation and pathological angiogenesis. In these models, NF- κ B, IL-6, and TNF- α are upregulated, paralleling the neovascularization observed in human PDR[49]. Thus, inflammation contributes not only to early microvascular dysfunction but also to advanced PDR changes. Beyond vascular injury, systemic and retinal inflammation profoundly affect the neurosensory retina. VEGF, while pathologically involved in angiogenesis, also has neuroprotective properties, promoting axonal growth, neuronal differentiation, and survival[50]. Insulin likewise exerts neurotrophic effects, with systemic and local administration rescuing retinal neurons in diabetic models[51]. Other protective mediators include neuroprotectin-D1, brain-derived neurotrophic factor, glial cell line-derived neurotrophic factor, ciliary neurotrophic factor, and nerve growth factor[52]. While these factors may initially serve compensatory roles, chronic upregulation becomes maladaptive, contributing to BRB disruption and sustained inflammation.

Emerging evidence shows that retinal neurons themselves adopt a pro-inflammatory phenotype under hyperglycemia, producing mediators such as cyclooxygenase 2, inducible nitric oxide synthases, and ICAM-1[53]. Photoreceptors, due to their high metabolic demand, generate significant oxidative stress and amplify local cytokine production, further activating leukocytes and endothelial cells[53]. From a therapeutic standpoint, targeting inflammation has yielded encouraging outcomes. In experimental models, baicalein, a bioactive compound of plant origin, was shown to attenuate cytokine overexpression, reduce vascular leakage, and protect against ganglion cell loss in diabetic rats[54]. Similarly, minocycline, a derivative of the tetracycline class, exerted neuroprotective effects by suppressing microglial activation and caspase-3 activity, whereas doxycycline maintained visual function in patients with NPDR. However, not all interventions targeting inflammation fully prevent DR-related damage. For instance, deletion of CD40 or inducible nitric oxide synthases reduced vascular injury but did not restore normal retinal function. Similarly, inhibition of the receptor for advanced glycation end products signaling reduces inflammation without preventing vision loss. These findings highlight that while inflammation is pivotal, it acts in concert with other pathogenic pathways, such as oxidative stress. **Figure 1** schematically illustrates these interconnected inflammatory and degenerative mechanisms in DR.

Overall, systemic and intraocular inflammation drive multiple aspects of DR pathogenesis, from endothelial dysfunction and leukostasis to angiogenesis and neurodegeneration. However, given the complexity of cytokine signaling, single-target interventions may not suffice. Future therapeutic strategies will likely require a combined approach that selectively modulates key inflammatory nodes while addressing parallel mechanisms, such as oxidative stress.

LIPID METABOLISM AND RETINAL HEALTH

Although hyperglycemia is the principal driver of DR, increasing evidence indicates that lipid metabolism plays a significant role in retinal injury and disease progression. In fact, disruptions in lipid metabolism collaborate with inflammatory agents to exacerbate oxidative and endothelial stress in the diabetic retina[55]. Historical observations linked serum lipids to hard exudates and retinopathy, findings subsequently reinforced by dietary markers[55,56]. Notably, fenofibrate therapy was associated with a reduced requirement for laser treatment over 5 years[57]. In addition, its combination with simvastatin significantly slowed the progression of DR[58]; nonetheless, the benefits of fenofibrate did not map neatly onto improvements in conventional plasma lipid fractions, suggesting retina-intrinsic mechanisms beyond systemic triglyceride or high-density lipoprotein/Low-density lipoprotein (LDL) changes.

Diabetes perturbs systemic lipid handling through insulin resistance, elevating free fatty acids, triglycerides, and LDL while suppressing high-density lipoprotein[59]. At the same time, lipid regulation within the retina is highly specialized. It diverges from circulating profiles: Most retinal cells (notably Muller glia and photoreceptors) actively remodel fatty acids and maintain cholesterol balance through pathways that are partly autonomous from the circulation[4,60]. These dual (systemic and tissue-specific) alterations help explain why epidemiologic links between plasma lipids and microvascular complications are inconsistent compared with those for macrovascular disease[61].

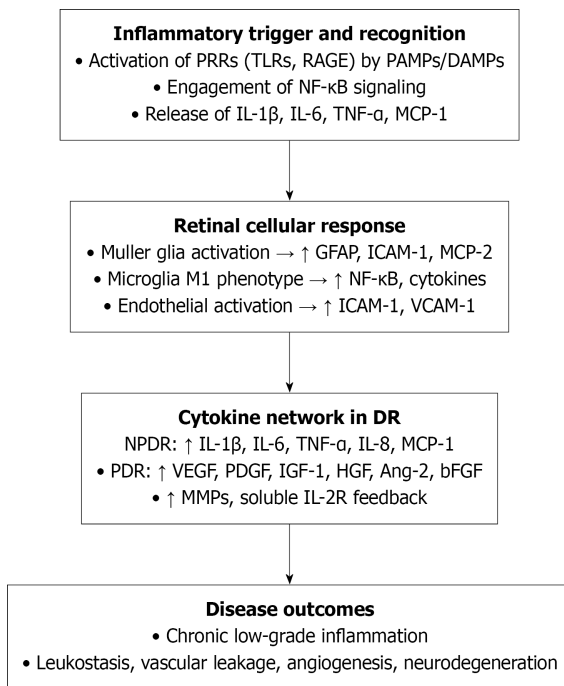


Figure 1 The figure illustrates how, in diabetic retinopathy, chronic inflammation bridges metabolic stress to retinal vascular and neuronal injury. Activation of Toll-like receptor/receptor for advanced glycation end products-nuclear factor kappa B signaling triggers cytokine cascades, glial activation, and endothelial dysfunction, ultimately leading to leukostasis, vascular leakage, angiogenesis, and neurodegeneration. PRRs: Pattern recognition receptors; TLRs: Toll-like receptors; RAGE: Receptor for advanced glycation end products; PAMPs: Pathogen-associated molecular patterns; DAMPs: Damage-associated molecular patterns; NF-κB: Nuclear factor kappa B; IL: Interleukin; TNF-α: Tumor necrosis factor-alpha; MCP: Monocyte chemoattractant protein; GFAP: Glial fibrillary acidic protein; ICAM-1: Intercellular adhesion molecule 1; VCAM-1: Vascular cell adhesion molecule 1; DR: Diabetic retinopathy; NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; VEGF: Vascular endothelial growth factor; IGF-1: Insulin-like growth factor-1; HGF: Hepatocyte growth factor; Ang-2: Angiopoietin 2; bFGF: Basic fibroblast growth factor; MMPs: Matrix metalloproteinases; PDGF: Platelet-derived growth factor.

A consistent change in diabetes is the remodeling of retinal fatty acids. Retinal saturated and unsaturated species undergo elongation and desaturation; diabetes downregulates key elongases, thereby lowering docosahexaenoic acid, the dominant retinal n-3 polyunsaturated fatty acids (PUFA)[62]. Docosahexaenoic acid and its derivatives exert anti-inflammatory and anti-apoptotic actions and give rise to pro-resolving mediators. In diabetes, the balance shifts toward n-6 PUFA-derived eicosanoids *via* cytochrome P450 (CYP), lipoxygenase, and cyclo-oxygenase pathways, and soluble epoxide hydrolase (sEH). This activity further skews oxylipin profiles toward pro-inflammatory diols[63]. Supplementation with n-3 PUFAs reduces retinal vascular damage and pathological angiogenesis in models of diabetes, strengthening the therapeutic rationale for restoring PUFA tone[64].

Cholesterol homeostasis in the retina is equally complex. Unlike the brain, which relies almost entirely on local synthesis, the retina obtains cholesterol both *via* local biosynthesis and *via* LDL receptor-mediated uptake across the retinal pigment epithelium (RPE) from the choroidal circulation; intact inner BRB normally restricts nonspecific lipoprotein entry[65]. In diabetic retina, early inner BRB breakdown facilitates extravasation of plasma lipoproteins, while heightened LDL flux across RPE and capillary leakage raises intraretinal cholesterol burden[66]. Efflux occurs through reverse cholesterol transport governed by ATP-binding cassette transporter A1/G1 (ABCA1/ABCG1) and by CYP metabolism to more soluble oxysterols (CYP27A1, CYP46A1)[67]. Disruption of these output routes leads to cholesterol accumulation, oxysterol generation, and inflammatory activation. Oxidized/glycated LDL, as well as 7-ketocholesterol, are cytotoxic to pericytes and RPE and have been implicated in DR lesions[68]. Activation of liver X receptors (LXRs) restores ABCA1/ABCG1, dampens inflammation, and prevents acellular capillary formation; sirtuin 1-mediated LXR deacetylation similarly augments cholesterol export and protects against neural and vascular injury[69].

Sphingolipid metabolism adds another lipid axis relevant to DR. Diabetes shifts the ceramide spectrum from protective to pro-apoptotic, pro-inflammatory ceramides. The latter are largely generated by acid sphingomyelinase (ASM), which is upregulated in the diabetic retina; concurrently, elongase-VL4 (ELOVL4) downregulation limits very long-chain fatty acid supply for very long-chain ceramide synthesis, tipping the balance toward barrier breakdown and leakage[70]. Fenofibrate not only engages peroxisome proliferator-activated receptor-alpha (PPARα) but also globally lowers circulating ceramides; the lysosomal ASM-linked ceramide species (C16, C18, C24:1) that predict plaque instability systemically are likewise elevated in the diabetic retina, underscoring shared pathobiology[71]. Mitochondria from diabetic retinas accumulate ASM-derived sphingomyelin ceramides and display impaired respiratory control, deficits that are reversible by ASM inhibition, implicating ceramide-driven mitochondrial dysfunction in retinal pathology[72].

These mechanistic threads converge on therapeutic implications. PPARα is downregulated across retinal layers in both DM1 and DM2; its activation by fenofibrate provides endothelial cells, pericytes, and RPE with anti-inflammatory and anti-apoptotic protection, reduces vascular leakage and inflammation, and is neuroprotective, effects that are largely

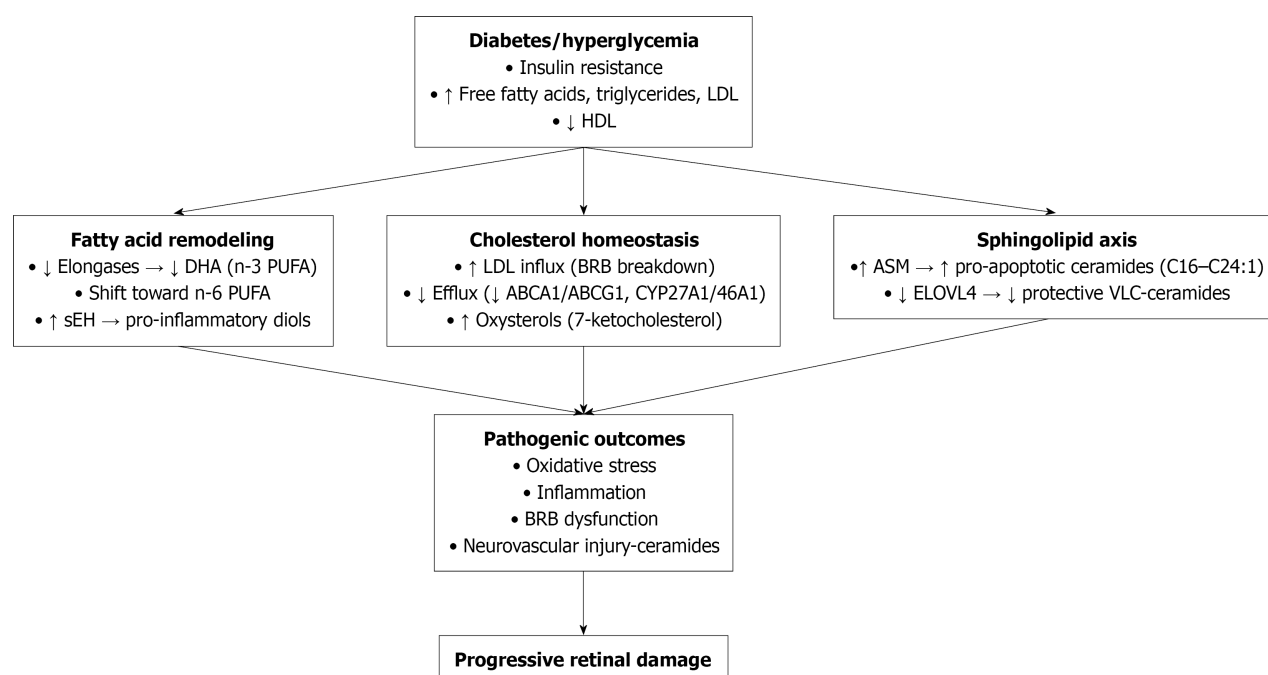


Figure 2 The figure illustrates how diabetes alters systemic and retinal lipid pathways, fatty acid remodeling, cholesterol turnover, and sphingolipid balance, driving oxidative stress, inflammation, and barrier breakdown. LDL: Low-density lipoprotein; HDL: High-density lipoprotein; DHA: Docosahexaenoic acid; PUFA: Polyunsaturated fatty acids; sEH: Soluble epoxide hydrolase; BRB: Blood-retinal barrier; ABCA1/ABCG1: ATP-binding cassette transporter A1/G1; CYP27A1/46A1: Cytochrome P450 27A1/46A1; ASM: Acid sphingomyelinase; ELOVL4: Elongases-VL4; VLC: Very long chain.

independent of systemic lipid lowering[73]. LXR agonism enhances cholesterol efflux and limits NF- κ B signaling, while targeting sEH and ceramide production (*e.g.*, ASM inhibition) further normalizes lipid-driven inflammatory tone[74]. By contrast, population-level signals for statin benefit remain suggestive but inconclusive in the absence of large randomized DR-focused trials[75].

The efficacy of statins in preventing DR remains contentious. Although observational studies indicate a slight decrease in DR progression, extensive prospective trials have produced mixed results. Mechanistic explanations encompass restricted statin diffusion across the BRB, inadequate control of retinal-specific lipid transport, and the possibility that the beneficial vascular effects of statins are offset by their influence on glucose metabolism. These inconsistencies highlight the necessity for lipid-modulating strategies that specifically target retinal lipid transporters (ABCA1/ABCG1) and nuclear receptors (LXR, PPAR α) rather than solely on systemic cholesterol[57].

In summary, DR reflects intertwined disturbances in fatty acid remodeling, cholesterol turnover, and sphingolipid balance that amplify oxidative stress, inflammation, barrier dysfunction, and neurovascular injury. The dissociation between fenofibrate's retinal benefits and changes in classical plasma lipids strongly argues for retina-intrinsic lipid mechanisms, intraretinal LDL influx/handling, efflux failure (ABCA1/ABCG1, CYP27A1/CYP46A1), maladaptive oxylipin signaling, and ceramide reprogramming as pivotal determinants of disease. Integrating lipid-focused strategies (n-3 PUFA repletion, PPAR α /LXR activation, sEH and ASM modulation) with glycemic control offers a rational path to modify the natural history of DR[5]. **Figure 2** illustrates how diabetes alters systemic and retinal lipid pathways, fatty acid remodeling, cholesterol turnover, and sphingolipid balance, driving oxidative stress, inflammation, and barrier breakdown.

THE GUT-RETINA AXIS

Recent evidence suggests that gut dysbiosis interacts with retinal tissues *via* metabolic and immune signaling, introducing a new aspect to the “beyond-glycemia” paradigm. Specifically, the interplay between the gastrointestinal tract and distant organs has been widely studied, most notably *via* the gut-brain axis, which represents bidirectional communication between the gut and the central nervous system (CNS)[2]. While this pathway was initially considered to mediate CNS control over gastrointestinal functions primarily, several studies highlighted how gut microbiota can also modulate the initiation and progression of neurological diseases[16,76]. In the enteric nervous system, illustrative examples include the detection of amyloid plaques and neurofibrillary tangles (hallmarks of Alzheimer's disease)[18], as well as the presence of Lewy bodies, characteristic of Parkinson's disease, in intestinal neurons[76].

Because the retina is both anatomically and developmentally derived from the brain[77], it has been proposed that microbial influences originating in the gut may also extend to retinal tissues[78]. The retina exhibits multiple parallels with the CNS, such as its layered neuronal architecture derived from the neural tube. Neurodegenerative phenomena in the CNS are frequently mirrored by retinal alterations[79]. Early Alzheimer's disease has been correlated with retinal

ganglion cell layer thinning[80], while progressive retinal neurodegeneration is a key factor in the pathogenesis of vision-threatening diseases, including glaucoma, age-related macular degeneration (AMD), and DR[81]. These converging observations have fueled the hypothesis of a gut-retina axis, distinct from but analogous to the gut-brain axis, capable of shaping ocular physiology and pathology[82]. Recent investigations have indeed confirmed that gut microbial composition can influence the development of ocular disease[83,84]. The concept was formally proposed as a regulatory pathway governing ocular immune homeostasis, with implications for conditions including AMD[85], uveitis[86], glaucoma[87], and DR[2,3]. The intestinal-ocular axis thus represents a novel and rapidly expanding field in ophthalmology[88].

Emerging evidence indicates that the gut microbiota regulates retinal homeostasis through multiple systemic mechanisms, including modulation of inflammation, shaping of immune responses, preservation of gut barrier integrity, and control of cellular trophism[89]. Perturbations such as dietary imbalance, pharmacological exposure, psychological stress, and aging contribute to dysbiosis, leading to metabolic disturbances and increased systemic inflammation. Microbial metabolites, endotoxins, reactive oxygen species, and cytokines act as mediators of this cross-talk[19]. Moreover, gram-negative bacteria release extracellular vesicles and outer membrane vesicles that transport proteins, lipids, nucleic acids, and small RNAs, thereby mediating molecular communication between distant organs[90]. Experimental studies demonstrated that outer membrane vesicles administered orally can translocate from the gut to multiple tissues, including the brain[91], raising the possibility that similar mechanisms could influence the retina. Extracellular vesicles have been shown to regulate immune activity and inflammatory cascades[92], while bacterial small RNAs may directly modulate eukaryotic gene expression[93]. These mechanisms suggest that retinal tissues, like the brain, could be directly affected by microbiota-derived vesicular communication.

Dysbiosis is increasingly linked to the pathogenesis of DR, a vision-threatening complication of diabetes characterized by hyperglycemia-induced oxidative stress, vascular leakage, and neovascularization[94]. Altered microbial profiles have been described in DR patients, including reductions in *Actinobacteria* and *Bacteroidetes* with increased *Escherichia* and *Prevotella*[95]. Other studies, however, reported increased *Bacteroidetes*, highlighting the absence of a uniform microbial signature[96]. Mendelian randomization studies identified certain taxa, such as *Christensenellaceae*, as protective, whereas *Eubacterium rectale* and *Ruminococcaceae* UCG-011 were associated with an increased risk of DR[97]. Moreover, the loss of beneficial species such as *Butyricoccus* has been linked to decreased plasma SCFA levels[98], which compromise gut barrier function and exacerbate systemic inflammation[99,100].

SCFAs, notably butyrate and propionate, demonstrate anti-inflammatory properties by activating G-protein coupled receptors (GPR41, GPR43, and GPR109A) found on retinal microglia and endothelial cells. Their downstream signaling inhibits NF- κ B activation and facilitates the differentiation of regulatory T cells. Concurrently, SCFAs impede histone deacetylases, thus enhancing chromatin accessibility for anti-inflammatory transcription factors. Preclinical findings indicate that butyrate or acetate supplementation mitigates microglial activation, diminishes VEGF and IL-1 β production, and maintains retinal barrier integrity in diabetic mice, highlighting a molecular connection between the gut and retina [16,17].

Experimental and clinical studies further highlight the functional impact of dysbiosis on DR progression. Gut microbiota influences retinal neurodegeneration[101], inflammatory signaling[95], glucose metabolism, and insulin resistance[96]. Conversely, retinal pathology itself can alter microbial communities, generating a feedback loop that exacerbates disease progression[99]. The depletion of carnosine, a dipeptide with antioxidant and anti-inflammatory activity, observed in DR patients[102], provides evidence that gut metabolites directly mediate gut-retina communication.

Increased intestinal permeability, a hallmark of dysbiosis, facilitates microbial translocation into systemic circulation. Commensal bacteria have been identified in atheromatous plaques[76], and microbial components have been found in the retinas of patients with retinitis pigmentosa and congenital amaurosis, both degenerative diseases[95]. Beyond bacteria, virome and mycobiome alterations may also contribute to ocular pathology. The gut harbors more than 140000 phages, many of which are uncharacterized, and phage imbalance has been associated with metabolic and inflammatory diseases [92]. Similarly, fungal communities influence microbial equilibrium, and dysbiosis of the mycobiome has been directly correlated with DR in humans and animal models[103].

Together, these findings delineate the gut-retina axis as a novel framework for understanding the interplay between systemic homeostasis and ocular pathology. Dysbiosis amplifies systemic inflammation, alters immune function, and disrupts metabolic and barrier integrity, thereby accelerating DR onset and progression. Although the precise molecular pathways remain incompletely understood, mounting evidence suggests that microbial metabolites, extracellular vesicles, and multi-kingdom microbial interactions mediate this communication. Recognition of the gut-retina axis opens a promising frontier in ophthalmic research, with implications for biomarker discovery, disease prediction, and microbiota-targeted therapies.

Current translational initiatives have investigated probiotics, prebiotics, and fecal microbiota transplantation to reestablish gut-retina equilibrium. Preliminary clinical investigations have demonstrated improvements in systemic inflammatory markers and retinal microvascular responsiveness; yet, persistent microbial engraftment, strain specificity, and long-term safety remain significant obstacles. Future trials necessitate consistent formulations, mechanistic biomarker endpoints (*e.g.*, SCFAs, circulating lipopolysaccharide), and association with optical coherence computed tomography angiography metrics to establish causality. **Figure 3** illustrates how gut dysbiosis disrupts intestinal and systemic homeostasis, leading to inflammatory and metabolic signals that reach the retina and promote neurovascular damage.

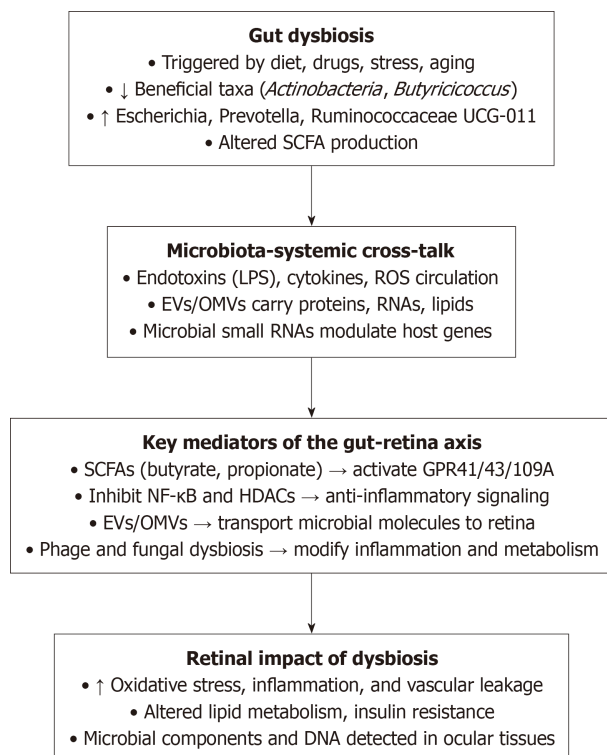


Figure 3 The figure illustrates how gut dysbiosis disrupts intestinal and systemic homeostasis, leading to inflammatory and metabolic signals that reach the retina and promote neurovascular damage. SCFA: Short chain fatty acids; LPS: Lipopolysaccharide; ROS: Reactive oxygen species; EVs: Extracellular vesicles; OMVs: Outer membrane vesicles; GPR: G-protein coupled receptors; HDAC: Histone deacetylases; NF-κB: Nuclear factor kappa B.

FUTURE PERSPECTIVES AND THERAPEUTIC IMPLICATIONS

The management of DR is progressively shifting from an exclusive focus on hyperglycemia and hypertension control toward a multifactorial and integrative strategy that acknowledges the pivotal roles of systemic inflammation, lipid metabolism, and the gut-retina axis. Several authors have indicated that chronic low-grade inflammation is a critical determinant of neurovascular dysfunction in DR[2,3]. In this context, gut microbiota dysbiosis is a major contributor to systemic and retinal pathology through mechanisms involving intestinal barrier disruption, microbial translocation, and reduced production of beneficial metabolites such as SCFAs[5,16,104]. These alterations amplify systemic endotoxemia, promote the induction of the innate immune system, and disrupt BRB integrity, thereby fueling microvascular leakage, gliosis, and neuronal apoptosis[3,4,16].

Therapeutically, this growing body of evidence supports the rationale for microbiota-targeted therapy. Strategies modulating the gut microbiome have proven effective in re-establishing microbial homeostasis and mitigating systemic inflammation in preclinical and early clinical research[16,104]. Precision nutritional strategies are equally promising: Mediterranean-style diets enriched in PUFAs have been shown to reduce the risk of vision-threatening DR by nearly 50% in older patients with DM2[57]. Mechanistically, omega-3 PUFAs gives rise to resolvins, protectins, and elovonoids, bioactive lipid mediators with strong anti-inflammatory and pro-resolving properties, counteracting the diabetes-induced predominance of pro-inflammatory omega-6-derived metabolites[58,64]. These findings point to dietary interventions not only as preventive strategies but also as potential adjunctive therapies to slow retinal degeneration.

Parallel advances have reinforced the role of dyslipidemia as a modifiable risk factor in DR. While observational studies have yielded inconsistent associations between circulating lipids and retinopathy, interventional trials have demonstrated that lipid-modifying drugs can positively influence retinal outcomes. Fenofibrate, an agonist of peroxisome PPAR α , showed beneficial effects in the FIELD and ACCORD Eye studies, where it reduced the need for laser therapy and delayed the progression of DR, effects that appeared to occur independently of changes in circulating lipid profiles [57,75]. Mechanistic studies suggest that fenofibrate exerts protective effects by enhancing retinal cholesterol efflux, decreasing ceramide accumulation, and suppressing inflammatory pathways within the retina[58,69]. Statins, while less consistently effective, have been associated with reduced incidence of DR and vision-threatening complications in large population-based cohorts, though randomized clinical trial data remain limited[57].

At the molecular level, therapeutic innovation has progressively focused on danger-sensing and resolution mechanisms rather than individual transcripts. In retinal microglia and Muller cells, activation of the NLR family pyrin domain-containing 3 (NLRP3) inflammasome has facilitated the release of IL-1 β /IL-18 and pyroptotic signaling; targeted inhibition of the inflammasome or caspase-1 has mitigated leakage and neuroinflammation in experimental diabetes[69]. Simultaneously, reinstating cholesterol efflux (LXR-ABCA1/ABCG1) and inhibiting ASM-ceramide synthesis have recalibrated the lipid-immune equilibrium and mitochondrial functionality[5,69]. In contrast, the suppression of sEH has

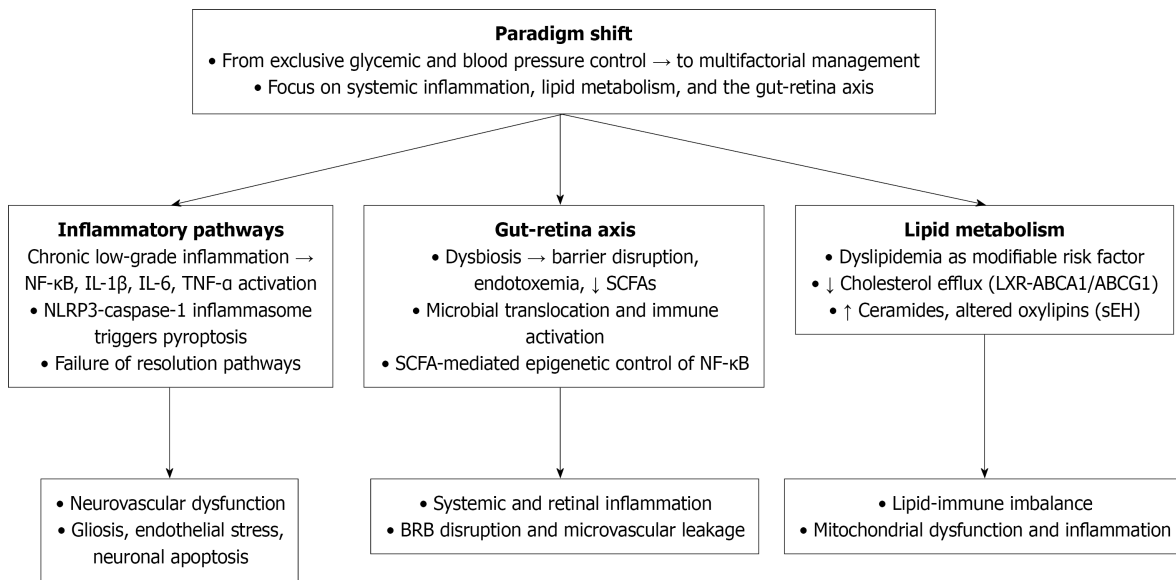


Figure 4 The figure outlines the shift toward a multifactorial view of diabetic retinopathy, where inflammation, lipid imbalance, and gut dysbiosis interact to drive neurovascular dysfunction. These interconnected pathways link metabolic stress to retinal inflammation, barrier disruption, and neuronal injury, redefining diabetic retinopathy as a systemic immune-metabolic disease beyond hyperglycemia. NF-κB: Nuclear factor kappa B; IL: Interleukin; TNF-α: Tumor necrosis factor-alpha; NLRP3: NLR family pyrin domain-containing 3; SCFA: Short chain fatty acids; BRB: Blood-retinal barrier; LXR: Liver X receptors; ABCA1/ABCG1: ATP-binding cassette transporter A1/G1; sEH: Soluble epoxide hydrolase.

redirected oxylipins towards pro-resolving mediators. SCFAs and associated postbiotics have imparted epigenetic signals (modulation of histone deacetylases) that have attenuated NF-κB-mediated transcription[16]. Collectively, these axes have identified prioritized objectives for initial human investigations, whereas small-RNA therapeutics have remained in the exploratory phase, awaiting sustainable, organ-specific delivery and safety data[104].

We prioritize the NLRP3-caspase-1, LXR-ABCA1/ABCG1, ASM-ceramide, and sEH-oxylipin signaling hubs for pharmacological interrogation, alongside efforts to quantify retinal oxysterols, ceramide species, and cytokine panels as biomarkers of target engagement. We also propose defined consortia or postbiotic formulations aimed at restoring SCFAs levels and epithelial barrier integrity, accompanied by systemic barrier readouts (*e.g.*, serum zonulin, circulating lipopolysaccharide) and eye-specific endpoints such as optical coherence tomography/optical coherence tomography-angiography (OCTA)-derived neurovascular metrics, to link gut reprogramming with retinal benefits mechanistically. Furthermore, we advocate for factorial or adaptive clinical designs integrating a lipid-targeted agent (*e.g.*, a PPARα agonist) with an anti-inflammatory or microbiota-modulating intervention, using OCTA measures, retinal layer thickness, and fluid biomarkers as early surrogates before assessing definitive vision-related outcomes.

The inflammatory component of DR pathogenesis remains a major therapeutic target. As highlighted by the concept of the “retinal neurovascular unit”, comprising neurons, glia, endothelial cells, and pericytes, successful treatments must address the neurodegenerative as well as the vascular components of the disease[2,3]. Anti-inflammatory agents such as salicylates, tetracycline derivatives (*e.g.*, minocycline, doxycycline), and novel small molecules have shown promise in reducing microglial activation, cytokine release, and neurodegeneration in experimental diabetes[2,4]. However, long-term efficacy and safety in clinical settings remain to be established. Future strategies may involve combination therapies integrating anti-inflammatory, lipid-modulating, and microbiota-targeted agents to achieve synergistic effects.

Looking ahead, the integration of multi-omics platforms (metagenomics, lipidomics, metabolomics, transcriptomics) with advanced imaging tools such as OCTA will provide new opportunities for personalized medicine in DR. These technologies could enable early identification of microbial or lipid signatures predictive of disease progression, thereby enabling patient stratification and individualized intervention[16,57,64,69]. In parallel, machine learning models incorporating microbiome, dietary, and immunological data already show potential for predicting DR onset and severity [5]. **Figure 4** outlines the shift toward a multifactorial view of DR, where inflammation, lipid imbalance, and gut dysbiosis interact to drive neurovascular dysfunction. These interconnected pathways link metabolic stress to retinal inflammation, barrier disruption, and neuronal injury, redefining DR as a systemic immune-metabolic disease beyond hyperglycemia.

COMPARATIVE THERAPEUTIC PERSPECTIVES AND CLINICAL SELECTION FACTORS

Among supplementary glycemic strategies, anti-inflammatory interventions, encompassing selective NLRP3 inflammasome inhibitors, IL-1β antagonists, and TNF-α blockers, show the most consistent mechanistic and preclinical validation, positioning inflammation control as the most advanced and actionable therapeutic avenue[69]. In contrast, lipid-modulating approaches, including fenofibrate and PPARα/LXR agonists, have demonstrated solid clinical efficacy and systemic safety. However, their translational impact is limited by poor BRB penetration and variable intraocular

Table 1 Pathogenic drivers and therapeutic perspectives in diabetic retinopathy

Intervention/target	Reported effects on DR	Retinal mechanism	Evidence level	Representative studies
miRNAs	Dual suppression of VEGF-A and lipid-modulating effects	Suppresses pathological angiogenesis and ceramide accumulation	Preclinical/translational	Experimental studies on miRNA-lipid interaction[94]
Statins	Lower systemic cholesterol; pleiotropic anti-inflammatory effects	Suppresses DR incidence in patients' population	Low-moderate (observational; limited RCT data)	Population-based cohorts; mechanistic discussion[97]
ASM inhibitors (ceramide axis)	Pro-apoptotic, pro-oxidant ceramide accumulation impairs retinal function and BRB integrity	Suppresses vascular leakage and neuronal loss	Preclinical	ASM inhibition and ceramide modulation studies[70-72]
sEH inhibitors	Preserve anti-inflammatory epoxy fatty acids; normalize oxylipin signaling	Suppresses retinal inflammation and neovascularization	Preclinical	Diabetes-induced retinopathy models[68]
LXR agonists	Enhances ABCA1/ABCG1-mediated cholesterol efflux; suppresses NF-κB-driven inflammation	Suppresses inflammatory cytokines	Preclinical	Experimental retinal models[69]
n-3 PUFA (DHA/EPA, Mediterranean diet)	Precursors of resolvins, protectins, and maresins; anti-inflammatory and oxidative stress reduction; suppresses risk of proliferative DR	Suppresses vascular leakage, oxidative stress, and inflammation; complete DR progression risk reduction in observational cohorts	Moderate-high (preclinical + dietary intervention trials in T2D)	PREDIMED cohort; dietary intervention trials in T2D[64,106]
Fenofibrate (PPARα agonist)	Restores downregulated PPARα; cell-protective effects on endothelial cells; suppresses inflammatory and oxidative stress <i>via</i> cholesterol efflux	Suppresses need for laser therapy; slower DR progression	High (large RCTs + preclinical validation)	FIELD, ACCORD studies[57,58]

DR: Diabetic retinopathy; miRNA: MicroRNA; ASM: Acid sphingomyelinase; sEH: Soluble epoxide hydrolase; LXR: Liver X receptors; PUFA: Polyunsaturated fatty acids; DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acid; PPARα: Peroxisome proliferator-activated receptor alpha; VEGF-A: Vascular endothelial growth factor-A; BRB: Blood-retinal barrier; ABCA1/ABCG1: ATP-binding cassette transporter A1/G1; NF-κB: Nuclear factor kappa B; RCT: Randomized controlled trial; T2D: Type 2 diabetes.

bioavailability[57]. Microbiota-directed therapies, such as probiotics, prebiotics, and fecal microbiota transplantation, offer a more integrative mechanism, influencing both inflammatory and metabolic axes. Yet the evidence remains preliminary, and the long-term stability and safety of microbial engraftment warrant further study[105].

From a clinical perspective, treatment selection should be guided by systemic metabolic status, inflammatory burden, and comorbidities. Patients with elevated cytokine or C-reactive protein (CRP) levels may benefit most from anti-inflammatory therapies[69]. In contrast, those with dyslipidemia or metabolic syndrome are suitable candidates for lipid-targeted regimens such as fenofibrate[57]. Conversely, individuals with gut dysbiosis, gastrointestinal comorbidities, or recent antibiotic exposure may respond more favorably to microbiota modulation[105]. Future clinical trials should prioritize integrative or combination strategies addressing inflammatory, lipid, and microbial pathways in parallel, informed by multi-omic biomarkers and advanced retinal imaging endpoints (*e.g.*, OCTA-based neurovascular metrics). Table 1 provides an overview of the major pathogenic mechanisms implicated in DR and the therapeutic strategies targeting them.

CONCLUSION

In conclusion, future perspectives in DR management converge on the recognition that the disease represents a systemic, neurovascular disorder in which inflammation, lipid dysregulation, and gut microbiota imbalance are interdependent drivers. Targeting these interconnected pathways through integrative strategies, including microbiota restoration, lipid-targeted therapies, anti-inflammatory drugs, and precision nutrition, holds the promise of not only halting DR progression but also preventing other retinal disorders, such as AMD, glaucoma, and uveitis[2-5,16,17,57,58,64,69,75,106]. The next decade will be decisive in translating these mechanistic insights into effective clinical interventions, paving the way toward personalized and preventive ophthalmology.

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FOOTNOTES

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