

Review

Targeting the Gut-Retina Axis in Age-Related Retinopathies: Microbiome-Immunometabolic Pathways and Gerotherapeutic Perspectives

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[Received October 21, 2025; Revised December 25, 2025; Accepted December 27, 2025]

ABSTRACT: Age-related retinopathies refer to a spectrum of retinal disorders primarily associated with aging, characterized by chronic oxidative stress, sustained inflammatory responses, and progressive visual impairment. Aging significantly influences the gut-retina axis by altering the gut microbiota and increasing intestinal permeability, thereby contributing to retinal pathology. The gut microbiota undergoes continuous coevolution with the host, and its composition and function are altered with advancing age. A persistent imbalance within the gut microbial community, known as dysbiosis, can increase intestinal permeability. This thereby allows microbes and their metabolites to more easily cross the epithelial barrier. These microbiota and metabolites can migrate to the retina via the gut-retina axis, potentially eliciting inflammatory responses and immune dysregulation. Such mechanisms have been involved in the occurrence and progression of diverse age-related retinopathies. This review delves into these bidirectional interactions within the gut-retina axis and their intricate implications for the pathogenesis of age-related retinopathies. A central focus is the pivotal role of gut microbiota and their metabolites in inducing retinal inflammation and immunological dysregulation. We endeavor to elucidate the synergistic mechanisms through which the neural, immune, and endocrine systems influence the pathology of age-related retinopathies. Furthermore, recent therapeutic trials targeting gut microbiota for the management of retinopathy are also discussed. These findings would provide novel insights and robust theoretical foundation for future advancement of innovative therapeutic strategies.

Keywords: age-related retinopathy, oxidative stress, gut-retina axis, gut microbiota, metabolites

1. Introduction

The global population is undergoing rapid aging, highlighting the imperative to elucidate the fundamental mechanisms of age-related diseases [1]. Accumulating evidence establishes the gut microbiota as a central modulator of host metabolism and immune function, which is deeply implicated in the aging process. A key feature of this process is a chronic, low-grade, systemic

inflammatory state known as “inflammaging” [1-2]. Each individual's gut microbiota exhibits unique characteristics and undergoes dynamic alterations in response to various factors such as lifestyle patterns, daily activity patterns, body mass index (BMI), dietary habits, and human aging [3]. The gut microbiota shares a vital link to gastrointestinal health, and its dysregulation has been implicated in a spectrum of pathological conditions, including inflammatory bowel disease (IBD), irritable

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bowel syndrome (IBS), and celiac disease (CD) [4]. Emerging evidence demonstrates that the effects of the gut microbiota reach well past the digestive system, potentially exerting significant effects on distal organs, particularly the visual system [5]. The systemic influence can be driven by age-related alterations in the host, as the landscape and functional potential of the gut microbiota undergo visible changes with advancing age [6]. The aging gut ecosystem undergoes a decline in the beneficial, short-chain fatty acids (SCFAs)-producing microbes and a concurrent rise in pro-inflammatory taxa. The consequent SCFAs deficit compromises the intestinal barrier by dampening the energy supply which is necessary for colonic epithelial function and integrity [7]. This increased gut permeability allows bacterial products like lipopolysaccharide (LPS) to translocate into circulation, thus triggering a state of systemic inflammation [7]. The inflammation subsequently propagates to the retina, inducing local oxidative stress, compromising the expression of critical visual proteins, and perturbing the tissue's immune homeostasis. These alterations collectively degrade retinal structural integrity and are posited to accelerate the progression of age-related retinopathies [8]. Notably, recent researches have established the gut-retina axis as a critical link between intestinal homeostasis and retinal health [8]. In the context of aging, the gut-retina axis can be defined as the bidirectional communications linking age-related gut dysbiosis with the pathogenesis of retinal diseases [9-10]. This axis functions as a key pathophysiological pathway that mediates the effects of the gut microbiota on retinal health through inflammaging and immune-related signaling pathway [9].

This review explores the complex molecular networks that mediate the bidirectional interactions between the gut microbiota and ocular health, giving particular attention to the gut-retina axis. We also intend to discuss the mechanism through which gut dysbiosis and microbiota-derived metabolites contribute to age-related retinopathies. Recent advancements in therapeutic strategies targeting gut microbiota to manage ocular diseases are also introduced in this review. These findings not only enrich our knowledge of gut-retina axis, but also offer a robust foundation for developing innovative therapeutic applications to preserve ocular health.

1.1 Literature selection strategy

This review comprises articles evaluating the bidirectional interactions between aging and gut-retina axis published from 1996 to 2025. The literatures are identified by a systematic search of various databases (PubMed/MEDLINE, Google Scholar, Cochrane Library, and Web of Science) using key terms such as “gut-retina

axis,” “gut microbiota,” “retinopathies,” and relevant metabolites. The literatures included are restricted to original research articles, landmark clinical studies, and authoritative reviews that directly explore the role of gut microbiota in the pathogenesis and therapy of age-related retinopathies. Articles which are not written in English, lacking full-text availability, or without sufficient evidence are excluded.

2. Gut microbiota and retinal physiology

2.1 Taxonomic features of the gut microbiota

Gut microbiota is an indispensable part of the human body that evolves together with its host. The sophisticated ecosystem of gut microbiota consists of bacteria, archaea, fungi, viruses, parasites, and particular metabolites derived from microbial processes [11]. Specifically, the bacteria within the gut microbiota are classified into more than 1000 species. Among them, Firmicutes and Bacteroidetes account for between 80% and 90% of the total population [12]. The gut microbiota exhibits resilience to environmental disturbances, enabling the preservation of essential microbial species over extended durations. Nevertheless, elucidating the resilience mechanisms of this intricate intestinal ecosystem remains a significant challenge. This is largely because the critical tipping points that trigger shifts between distinct microbial community states are not yet accurately defined [13]. The gut microbiota engages in diverse interactions, including mutualism, commensalism, competition, amensalism, and symbiosis with the host. Collectively, these interactions constitute fundamental determinants of microbial community stability and resilience [14]. Functional redundancy, wherein different species occupy analogous functional niches and can substitute for one another, is a key feature of the gut microbiota. It represents a pivotal factor conferring stability and resilience to the ecosystem [15]. Despite the relative stability of the core gut microbiota in healthy individuals, genus-level distributions exhibit significant temporal and spatial heterogeneity along the gastrointestinal tract. For example, *Streptococcus* predominates in the distal esophagus, duodenum, and jejunum, whereas *Helicobacter pylori* (Hp) prevail in the gastric environment. Remarkably, over two-thirds of the entire human microbiota resides in the colon, where *Bacteroides*, *Bifidobacterium*, *Streptococcus*, *Enterobacteriaceae*, *Enterococcus*, *Clostridium*, *Lactobacillus*, and *Ruminococcus* predominantly colonize the lumen and are routinely detected through fecal analysis [8, 16].

2.2 Functional features of the gut microbiota

The gut microbiota has often been consistently referred to as “the invisible organ” or “the neglected organ” to underscore its pivotal role in systemic health [17]. The concept of “holobiont” is frequently employed to emphasize that the host (human body) and its associated microorganisms constitute an integrated and balanced biological system [18]. Extensive research has identified multiple relationships between the gut microbiota and the nervous, immune and endocrine systems [17]. In the nervous system, the gut microbiota regulates central nervous system (CNS) functions and behavioral patterns through diverse mechanistic pathways. For instance, In APP/PS1 transgenic mice modeling Alzheimer’s disease, supplementation with probiotics rich in gram-positive bacteria (such as *Bifidobacterium* and *Lactobacillus*) can improve cognitive functions like spatial memory by reducing brain amyloid- β (A β) deposition and inhibiting excessive microglial activation [19]. The vagus nerve constitutes a direct bidirectional neural pathway that bridges the gastrointestinal tract and the CNS. Microbial-derived metabolites, including butyrate and indole, activate vagal afferent signaling pathways through this neural connection, subsequently modulating CNS functions [20]. In the immune system, the gut microbiota is fundamental to host defense by stimulating intestinal epithelial cells to produce antimicrobial peptides (AMPs), including Reg3 γ , a C-type lectin. These AMPs interact with Toll-like receptors (TLRs) by detecting microbial-associated molecular patterns (MAMPs). This interaction restricts bacterial invasion across the epithelial barrier and helps establish a physical barrier zone approximately 50 micrometers thick on the gut mucosal surface [21]. In the endocrine system, the gut microbiota metabolizes dietary fibers to generate SCFAs. These SCFAs enhance insulin sensitivity through two primary mechanisms: activating free fatty acid receptors (FFAR2/FFAR3) and stimulating intestinal L cells to produce glucagon-like peptide-1 (GLP-1) and peptide YY (PYY). Additionally, microbial β -glucuronidase modulates estrogen levels by regulating the balance between free and conjugated estrogen [22]. Collectively, these findings position the gut microbiota as a central modulator of systemic homeostasis. It achieves this by orchestrating intricate crosstalk through the neuroimmune-endocrine axis.

2.3 Immune regulation by the gut microbiota

Dynamic interplay between the gut microbiota and host immunity is fundamental for sustaining gut equilibrium and regulating inflammatory responses [23]. The gut mucosal immune system comprises three essential components: the epithelial barrier combating gut pathogens, the lamina propria containing diverse immune cells, and Peyer’s patches facilitating antigen presentation

in the small intestine [24]. Gut microbiota produces numerous metabolites, such as SCFAs or LPS, capable of modulating intercellular communication between intestinal epithelial cells and the immune system [8]. Whereas SCFAs exert anti-inflammatory properties through the activation of G protein-coupled receptors (GPR43/41) combined with HDAC inhibition to foster regulatory T cells (Tregs) differentiation [21]. LPS triggers TLR4-mediated nuclear factor kappa B (NF- κ B) signaling pathway activation, ultimately leading to massive production of pro-inflammatory cytokines [25]. Immune cells express specific receptors, including membrane-associated pattern recognition receptors (PRRs) like TLRs. These receptors bind directly to microbial components. This interplay is critical for the immune system’s capacity to preserve the host’s internal balance through tolerating the microbial burden (immunological tolerance), while staying responsive to pathogen incursion. This symbiotic relationship is contingent upon the precise discrimination between harmless (beneficial or neutral) and harmful microbes [26]. However, under certain conditions, such as impaired immune function, commensal bacteria may undergo a pathogenic transformation (commensal-to-pathogen transition) [8]. If the configuration of a balanced gut microbiota alters, the resulting gut dysbiosis would potentially promote the onset of various immune-related diseases [27].

2.4 The impact of gut dysbiosis on age-related retinopathies

The retina functions as an immune-privileged tissue, where its unique barrier system and immunomodulatory mechanisms collaboratively sustain the homeostasis of its microenvironment. The blood-retinal barrier (BRB), serving as the primary protective structure, comprises two components: the outer BRB, formed by tight junctions between retinal pigment epithelial (RPE) cells, which meticulously regulates substance exchange between the choroid and retina; and the inner BRB, analogous to the blood-brain barrier, constituted by retinal vascular endothelial cells through tight junctions and selective transport mechanisms [8, 28]. The retina’s immune privilege relies on a localized immunosuppressive microenvironment. This environment is characterized by decreased major histocompatibility complex (MHC) class II expression on retinal cells and the persistent secretion of immunomodulatory factors like vasoactive intestinal peptide. It also depends on specialized antigen-presenting cells (APCs) that promote immune tolerance rather than inflammation [29]. However, gut dysbiosis can disrupt the intestinal epithelial barrier, enabling the translocation of gut-derived components (microbial metabolites and

viable microbes) into systemic circulation. This process induces immune dysregulation and excessive pro-inflammatory cytokine secretion [30]. These elevated cytokines exert deleterious effects on RPE cells, disturb function of tight junctions, and dampen the stability of the BRB (Fig. 1). In this context, the compromised integrity of the BRB and the disruption of retinal homeostasis would facilitate the migration of circulating inflammatory

mediators and pro-angiogenic factors. These pathological alterations further exacerbate retinal neuroinflammation, promote aberrant vascular permeability, and ultimately lead to photoreceptor death and pathological neovascularization. Together, these processes constitute the hallmark features of age-related retinopathies, such as diabetic retinopathy (DR) and age-related macular degeneration (AMD) [30-31].

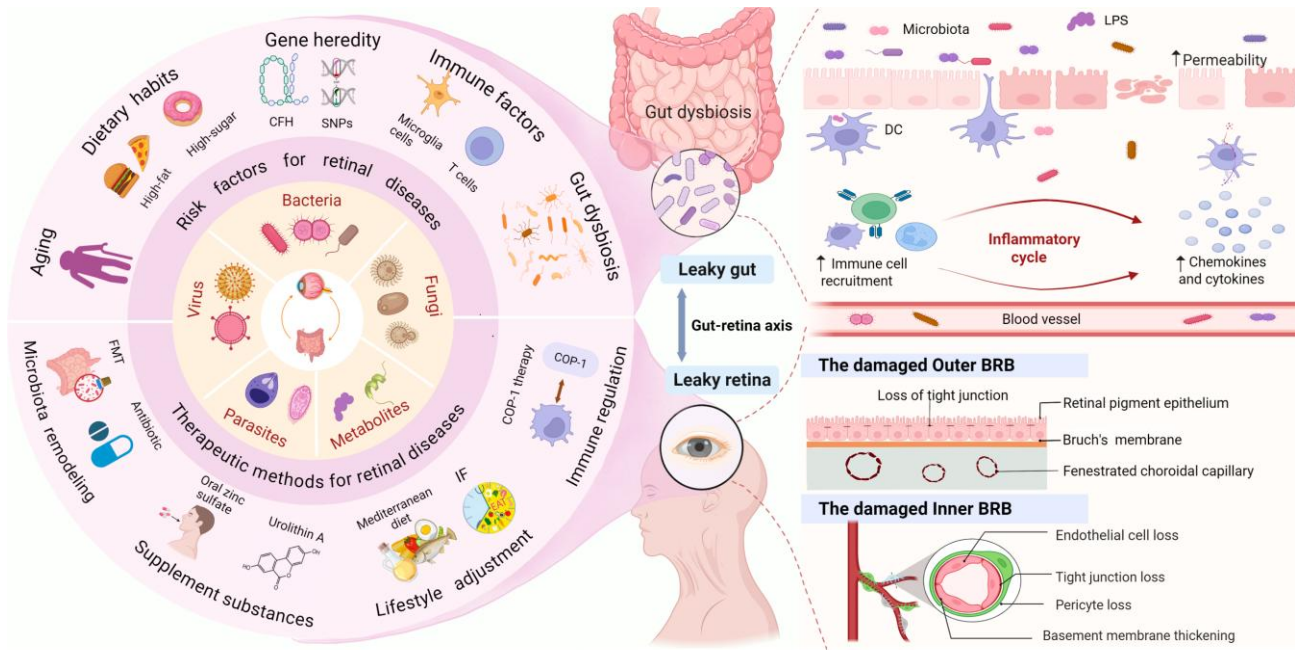


Figure 1. Multifaceted insights into retinal diseases: risk factors, treatment, and gut-retina axis pathology. The gut microbiota includes bacteria, fungi, viruses, parasites, and microbial metabolites. Retinal diseases involve diverse risks and treatments, with the gut-retina axis playing a key role (left). Gut dysbiosis compromises the intestinal barrier, allowing microbiota to enter the bloodstream, activating immune cells and triggering sustained inflammation. This disrupts both the outer and inner blood-retinal barriers, ultimately leading to a leaky retina and retinal disease (right).

2.5 Gut-retina axis

The gut dysbiosis can elicit pathological processes in extra-intestinal distal tissue through immune activation, metabolic dysregulation, barrier dysfunction, and neurohumoral secretion [32]. For instance, the gut microbiota can affect the synthesis and release of neurotransmitters through the gut-brain axis, thereby modulating mood, cognition, and behavior. Moreover, alternations in the gut microbiota can influence the metabolic and immune functions through the liver gut-liver axis [32]. In particular, recent investigations have uncovered the gut-retina axis, which represents a frontier in understanding the systemic microbiota-ocular interactions [8]. A pioneering clinical study has identified an age-associated increase in the Bacteroidetes-to-Firmicutes ratio in the gut microbiota. This microbial alternation correlates with the pathogenesis of AMD [33]. This compositional shift is particularly detrimental

because Bacteroidetes are gram-negative bacteria capable of generating LPS and flagellin, key MAMPs that trigger host immune responses [12]. A recent clinical study has shown that the population of butyrate-producing microbiota, particularly *Faecalibacterium prausnitzii*, is greatly decreased in the intestinal tract of DR subjects compared to healthy controls [34]. The study indicates that certain microbial populations can enhance insulin sensitivity and alleviate inflammatory responses via butyrate biosynthesis [34]. On the other hand, pharmacological interventions such as broad-spectrum antibiotic administration or fecal microbiota transplantation (FMT) are capable of alleviating the retinal pathologies [35-36].

Cumulatively, these findings have demonstrated the “gut-retina crosstalk” in human beings. However, the exact mechanism through which gut-retina axis modulates the pathology of retinopathies remains unclear. Some viewpoints propose that gut dysbiosis enhances intestinal

permeability, thereby facilitating bacterial translocation from the gut to the retina via the bloodstream or mesenteric lymphatic system [8, 30]. Besides, gut dysbiosis can activate innate immune cells within the gastrointestinal tract, particularly dendritic cells (DCs) and T helper 17 (Th17) cells. This activation subsequently triggers the production of pro-inflammatory cytokines, notably interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) [37]. This gut-derived inflammation may reach distant sites, even breach the BRB and infiltrate the retina [8]. Stemming from these research outcomes, the concept of the gut-retina axis has emerged to elucidate the importance of gut microbiota as significant modulators in

the development of retinopathy [8]. As a burgeoning bidirectional regulatory paradigm, it reveals intricate interactions between gut microbiota and retinopathies through multifaceted mechanisms, such as microbial metabolite translocation and immune-inflammatory cascade activation. This conceptual framework challenges conventional perspectives by establishing gut microbiota as active contributors rather than mere bystanders in the pathogenesis of retinopathies. Beyond deciphering the cross-organ pathogenic mechanisms linking the gut and retina, its scientific significance lies in uncovering the molecular basis of microbe-host interactions to pioneer microbiota-targeted diagnostic and therapeutic strategies.

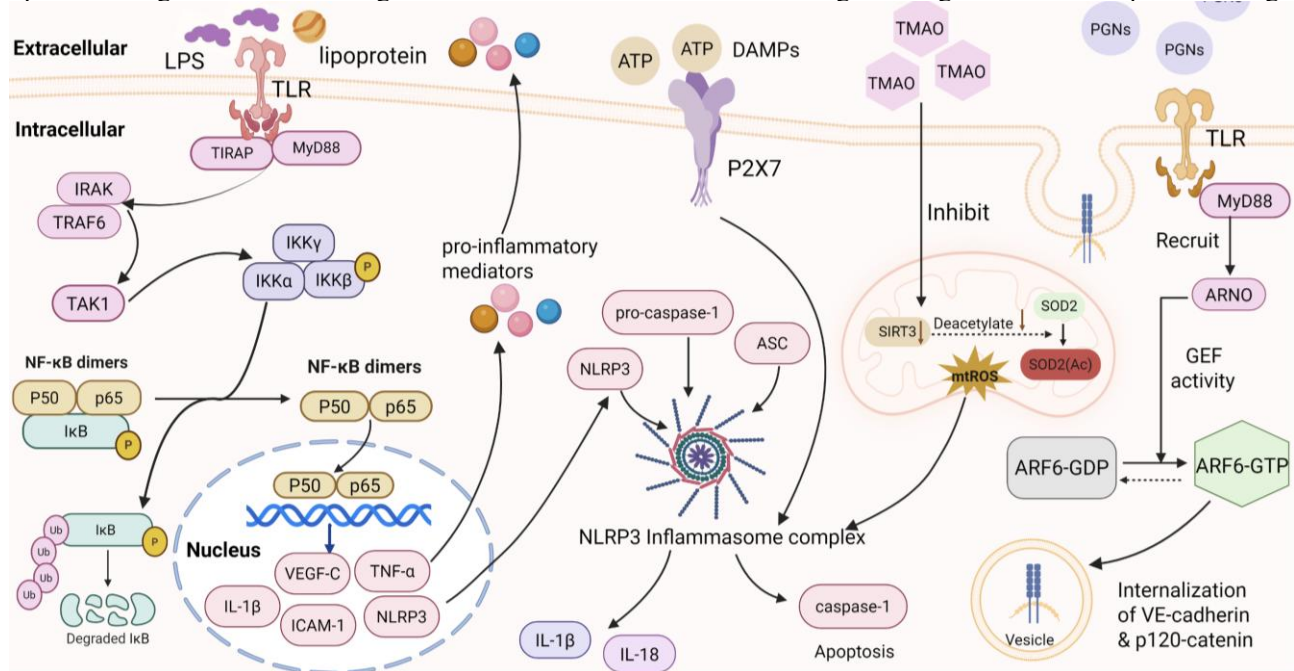


Figure 2. Core pathogenic pathways in age-related retinopathies. Integrated signaling network showing how gut-derived stimuli activate retinal pathology through interconnected axes: TLR4/NF- κ B signaling induces pro-inflammatory mediator expression and NLRP3 priming; mitochondrial oxidative stress via the TMAO-SIRT3-SOD2 axis and purinergic signaling through ATP-P2X7 provide activation signals for NLRP3 inflammasome assembly and IL-1 β /IL-18 maturation; and TLR2-ARNO-ARF6 signaling disrupts vascular integrity via internalization of junctional proteins. These pathways collectively promote neuroinflammation, vascular leakage, and pathological neovascularization. Note. Ac, acetyl; GEF, guanine nucleotide exchange factors.

2.6 Core pathogenic pathways in age-related retinopathy

Age-related retinopathies, including AMD and DR, are mediated through a complex signaling network that translates systemic pathological stimuli into retinal tissue damage. The core sequence of events begins with the activation of TLRs by gut-derived ligands. TLR engagement by LPS or lipoprotein recruits the adaptor proteins TIR domain-containing adaptor protein (TIRAP) and myeloid differentiation primary response 88 (MyD88), leading to the sequential activation of interleukin-1 receptor-associated kinases (IRAKs), TNF receptor-associated factor 6 (TRAF6), and transforming

growth factor β -activated kinase 1 (TAK1) [38]. TAK1 then phosphorylates the I κ B kinase (IKK) complex. This phosphorylation promotes the degradation of inhibitors of κ B (I κ B). Consequently, NF- κ B dimers are released and migrate to the nucleus, where they drive the production of key pro-inflammatory mediators, including TNF- α , IL-1 β , Intercellular adhesion molecule 1 (ICAM-1), and vascular endothelial growth factor C (VEGF-C), as well as the essential components of the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome [38-40] (Fig. 2). Concurrently, the NLRP3 inflammasome pathway is activated in two sequential steps. The initial step, known as “priming,” entails the

NF- κ B-mediated upregulation of NLRP3 and pro-IL-1 β [38]. The second step involves a distinct activation signal, such as mitochondrial reactive oxygen species (mtROS). Metabolites like trimethylamine N-oxide (TMAO) can generate this signal by downregulating the mitochondrial deacetylase sirtuin 3 (SIRT3), thereby inducing hyperacetylation and functional impairment of the antioxidant enzyme superoxide dismutase 2 (SOD2), which ultimately leads to mtROS accumulation [41]. Alternatively, extracellular Adenosine Triphosphate (ATP), derived from complement deficiency-induced metabolic reprogramming of the gut microbiota, acting on the P2X purinoceptor 7 (P2X7) receptor, provides another common activation signal [42]. Both stimuli trigger NLRP3 inflammasome assembly and caspase-1 activation, culminating in the maturation of IL-1 β and IL-18 [41-42] (Fig. 2). In a parallel pathway, TLR2 activation by peptidoglycans (PGNs) initiates a MyD88-dependent cascade that recruits ARF nucleotide-binding site opener (ARNO) to activate ADP-ribosylation factor 6 (ARF6). This activation then induces the internalization of the endothelial junction proteins vascular endothelial-cadherin (VE-cadherin) and p120-catenin, thereby directly compromising vascular integrity [43] (Fig. 2).

3. Gut microbiota and age-related macular degeneration

3.1 Etiologic factors of age-related macular degeneration

AMD is a leading cause of vision loss in older adults across developed countries. This condition specifically damages the macula, causing progressive and often permanent loss of central vision that can advance to severe visual impairment [8]. It is estimated that the patients with AMD will escalate to 288 million cases by the year 2040 [44]. Early AMD presents with drusen deposition within the RPE layer. In its late stages, the disease diverges into two distinct forms: geographical atrophy (dry AMD), characterized by plentiful depletion of the RPE and choriocapillaris; and neovascular AMD (wet AMD), manifested as the neovascular in the macular region, which results in fluid leakage or hemorrhage in fundus [45]. AMD pathogenesis is multifactorial, driven by a confluence of interrelated risk factors spanning age, environment, epigenetics, and genetics [8]. The advanced age acts as the most predominant risk factor for AMD [44]. Multiple genetic risk loci are associated with AMD, among which single nucleotide polymorphisms (SNPs) in the complement factor H (CFH) gene rank as the primary heritable determinant of AMD, followed by SNPs in the age-related maculopathy susceptibility 2 (ARMS2)/high-temperature requirement A serinepeptidase 1 (HTRA1)

gene [8]. Numerous studies have highlighted that dietary and nutritional factors can affect the progression of AMD. Mice fed the high-glycemic index (HG) diet develop characteristic AMD-like retinal pathologies, including photoreceptor degeneration, RPE atrophy, and lipofuscin accumulation [46]. HG diet induces gut dysbiosis that is characterized by the increased abundance of pro-inflammatory Clostridiales and the concomitant decrease in protective Bacteroidales [46]. The gut dysbiosis subsequently disrupts the metabolic homeostasis of retina, resulting in decreased protective metabolites (serotonin) and elevated oxidative stress markers, specifically the carboxyethylpyrrole (CEP) and 4-hydroxynonenal (4-HNE) [46]. Likewise, in murine models of laser-induced choroidal neovascularization (CNV), a high-fat diet (HFD) can exacerbate angiogenesis by promoting metabolic endotoxemia and systemic inflammation. This effect is mediated by HFD-induced gut dysbiosis, marked by a reduction in Bacteroidetes and an increase in Firmicutes. On the other hand, antibiotic treatment with neomycin can restore the dominance of Bacteroides and normalize CNV development. FMT from conventionally fed mice to HFD-fed animals reduces CNV by 35% [5]. Therefore, abnormal diets can induce gut dysbiosis, which in turn accelerates the development of AMD through various pathophysiological mechanisms.

3.2 Gut microbiota associated with age-related macular degeneration

Accumulating clinical evidence has substantiated a link between the composition of the gut microbiota and the pathogenesis of AMD. For instance, a comparative case-control analysis has revealed distinct gut microbial changes in AMD. Specifically, patients show markedly reduced α -diversity relative to age-matched healthy controls. Measured by the Simpson index, this indicates a decline in microbial community evenness [47]. In-depth analysis of taxonomic composition within the same cohort has identified elevated relative abundances of the genera Prevotella, Holdemanella, and Desulfovibrio, while the genera Dorea, Blautia, and Oscillospira are present at lower levels [48]. This profile aligns with observations from other studies in elderly AMD groups, where additional changes such as a decrease in Bacteroides eggerthii and an increase in the Firmicutes/Bacteroidetes ratio have been documented [49]. Consequently, these alterations may promote the progression of the AMD and potentially serve as the diagnosis biomarkers for AMD. Overall, the alterations in microbial community composition observed in these clinical cohort studies suggest the potential for significant changes in their metabolic functions. Metagenomic analysis detects 72 important microbial metabolic pathways in subjects with

AMD, with a marked upregulation in the carotenoid biosynthesis, lipid metabolism, fatty acid biosynthesis, and bacterial chemotaxis enrichment [50]. In particular, a recent study shows that the gut microbiota taxa correlating with AMD are enriched with the IgA-bound fraction and are implicated in the regulation of immune response [51]. Secretory IgA (sIgA), a pivotal effector in mucosal immunity, selectively coats IgA-bound microorganisms. It orchestrates host-microbiota interactions through suppressing proinflammatory pathobionts while maintaining commensal symbionts. This intricate binding

mechanism exemplifies the host's immune surveillance system, wherein IgA specifically targets microbial taxa to sustain intestinal homeostasis and avert systemic inflammation [52]. Dysregulated IgA-microbiota interaction may compromise immune tolerance, potentially activating inflammatory pathways associated with AMD pathogenesis [53]. In summary, the evidence collectively highlights that the alternation in gut microorganisms is closely associated with AMD pathogenesis.

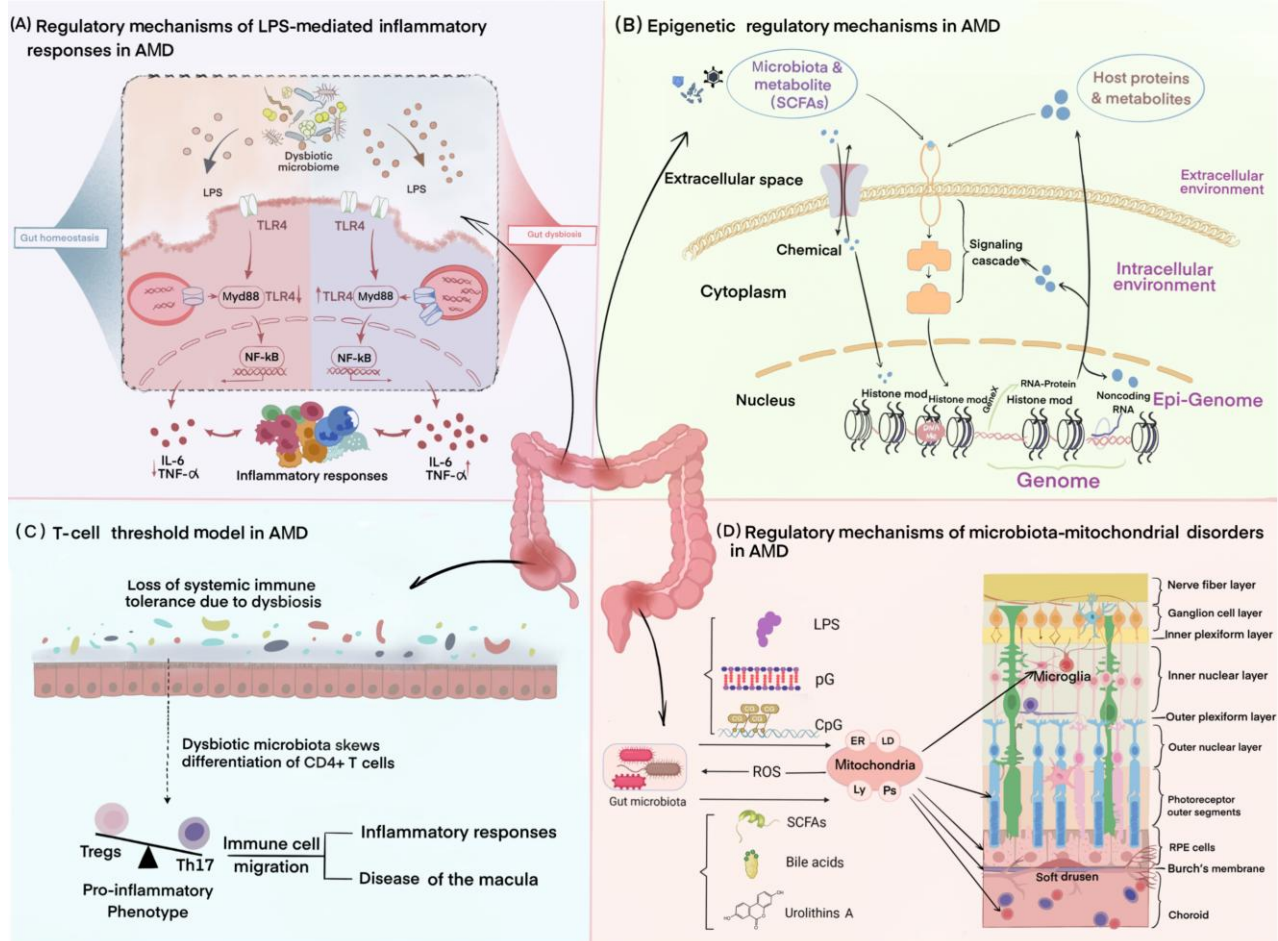


Figure 3. Regulatory mechanisms underlying AMD in the context of gut microbiota. (A) LPS-mediated inflammation: Dysbiosis increases LPS translocation, activating TLR4/NF-κB signaling and amplifying pro-inflammatory responses in AMD. (B) Epigenetic regulation: Microbial metabolites influence gene expression via DNA methylation, histone modification, and non-coding RNAs, affecting ocular immune homeostasis. (C) T-cell involvement: Dysbiosis promotes Th17 cell differentiation, leading to retinal inflammation and macular damage. (D) Microbiota-mitochondria crosstalk: Microbial metabolites (SCFAs) support retinal health, while endotoxins (LPS) induce oxidative stress and inflammation, contributing to early AMD.

3.3 Role of gut microbiota in the age-related macular degeneration

3.3.1 Gut dysbiosis and intraocular inflammation in age-related macular degeneration

Pioneering researchers have proposed that AMD is presumably caused by gut dysbiosis, which precipitates mucosal barrier dysfunction, and results in the translocation of pathogenic substance due to increased permeability of epithelial barrier [8]. For example, LPS can promote TLR4/NF-κB-driven expression of pro-inflammatory mediators, perpetuating retinal

inflammation [54] (Fig. 3A). It is noteworthy that gut dysbiosis may trigger epigenetic reprogramming events that contribute to inflammation reactions in AMD [55]. Microbial metabolites, particularly SCFAs, can modulate immune cell activity via epigenetic modifications. These intricate interactions may disrupt ocular immune homeostasis, thus potentially contributing to the onset and progression of AMD [55]. Specifically, extracellular stimuli, including microorganisms and their metabolites, can initiate a stimulus-specific signaling cascade. This process leads to epigenomic reprogramming, alterations in gene expression, and shifts in cellular functionality [55]. In particular, a recent study shows that the hypomethylation of the interleukin-17 receptor C (IL-17RC) promoter can enhance the IL-17-mediated inflammatory signaling in AMD. Nevertheless, this conclusion is still controversial, as an independent study could not reproduce the results in their sample. These findings highlight the possibility that gut microbiota may modulate the methylation status of other AMD-associated genes via metabolic-epigenetic mechanisms [55]. Therefore, these microbiota-epigenome interactions can disrupt ocular immune homeostasis and synergistically accelerate disease progression [55] (Fig. 3B). Gut dysbiosis can also result in the imbalance between pro-inflammatory Th17 cells and immunosuppressive Tregs, which subsequently drives the maladaptive immune differentiation in AMD. The enhanced presence of Th17 cells facilitates their translocation from the gut to distant sites, thereby exacerbating the inflammation in retina [56] (Fig. 3C). Additionally, a Mendelian randomization (MR) study has confirmed the causal role of Rhodospirillales in AMD risk [51]. While clinical evidence from AMD patients remains scarce, research conducted on pulmonary hypertension (PH) has demonstrated that Rhodospirillales is significantly enriched as a detrimental gut microbiota biomarker in mice with hypoxia-induced PH. Simultaneously, these mice display augmented levels of pro-inflammatory mediators, including IL-1 β . This indicates a potential association between the abundance of Rhodospirillales and the increase in pro-inflammatory cytokine levels under this pathologic condition [57]. These proinflammatory cytokines are well-established promoters of neovascularization and disruptors of the neurovascular unit (NVU) in AMD [51]. Consequently, researchers hypothesize that Rhodospirillales may be involved in the pathogenesis of AMD through the gut-retina axis, potentially via systemic inflammatory pathways [51].

3.3.2 Role of the complement system in age-related macular degeneration

Genetic insights have firmly established the complement system's central role in AMD pathogenesis. A genome-wide association study from the "Catalog of Human Genome-Wide Association Studies" have revealed 103 risk loci for AMD, highlighting CFH and ARMS2/HTRA1 as the two most significant [58]. This connection is further supported by work linking AMD to specific SNPs in genes encoding complement proteins, such as component 3 (C3), complement component 2 (C2), and complement factor B (CFB) [33, 59]. CFH serves as a regulatory protein in the complement cascade and is a genetic risk factor for AMD. SNPs in the CFH gene can cause an overstimulated or dysregulated complement system, leading to neurodegenerative diseases like AMD [60]. In particular, a recent genotype-phenotype analysis shows that individuals harboring the CFH Y402H variant exhibit heightened levels of membrane attack complex (MAC), which may initiate the inflammatory response and facilitate the advancement of AMD [61]. The gut microbiota in C3-deficient murine exhibit similar taxonomic features to that in neovascular AMD patients. For example, the ratio of Firmicutes to Bacteroidetes is elevated in C3-deficient murine relative to wild-type controls. It is highly possible that Firmicutes may contribute to the AMD pathologies in C3-deficient murine, whereas Bacteroidetes may exert a protective effect [33, 62]. The analysis of the murine gut microbiota has identified a significant increase in genes associated with the 5-aminoimidazole ribonucleotide (AIR) biosynthesis pathway in the C3-deficient murine. This increase suggests a potential compensatory mechanism where gut microbiota modulates their metabolic activity in response to host complement system deficiency [33]. This metabolic reconfiguration towards AIR biosynthesis, a crucial intermediate in purine metabolism, may hold significant implications for AMD pathogenesis. Purine metabolites like ATP can function as damage-associated molecular patterns (DAMPs) that initiate inflammatory responses through the activation of NLRP3 inflammasome and the subsequent production of IL-1 β [42] (Fig. 2). These processes are well-documented contributors to AMD progression. Taken together, these findings underscore the intricate interplay between host genetic factors (C3 deficiency), gut microbial metabolism, and retinal pathology. This interplay suggests that therapeutic interventions targeting specific microbial metabolic pathways could provide innovative approaches for AMD management.

3.3.3 Mitochondrial dysfunction in early age-related macular degeneration

Pioneering studies have introduced a novel concept pertaining to microbiota-mitochondrial dysfunction and

its contributory role in AMD [63]. The metabolites of gut microbiota, which include SCFAs, urolithins A(UAs), bile acids(BAs), and unmethylated CpG-containing oligonucleotides, have the potential to exert anti-inflammatory effects and positively impact mitochondrial metabolism and function [64]. As the SCFAs bind to G protein-coupled receptors (GPCRs), they will facilitate mitochondrial activity and biogenesis through the enhancement of mitochondrial oxidative phosphorylation and fatty acid β -oxidation, as well as the activation of the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1- α) signaling pathway. Concurrently, these compounds alleviate inflammation response by modulating immune responses and epithelial barrier integrity [63]. UAs improve mitochondrial function by stimulating mitophagy, reducing fragmentation, and upregulating mitochondrial fusion and synaptic genes [63]. Secondary BAs, taurodeoxycholic acid (TUDCA) and ursodeoxycholic acid (UDCA), exert cytoprotective effects through multifaceted mechanisms. They suppress mitochondrial membrane permeability transition pores (mPTP) to avert apoptosis and preserve mitochondrial integrity. They can also elevate the expressions of mitochondrial biogenesis-associated proteins and promote mitophagy. The augmented mitophagy will eliminate impaired mitochondria and synergistically maintain mitochondrial homeostasis [63]. In parallel, unmethylated CpG-containing oligonucleotides can attenuate inflammatory responses through TLR9 activation and enhance the phagocytic capacity of RPE cells [63]. On the other hand, both LPS and PGNs exert proinflammatory effects through activating the TLRs in microglia and RPE cells, triggering neuroinflammation, RPE dysfunction, and mitochondrial damages [19, 63, 65-66]. Mitochondria serve as the organelle target of microbiota derivatives and function as the energy powerhouse through the mitochondria contact sites (MCSs). The MCSs, which are comprised of an organelle-network encompassing mitochondria, endoplasmic reticulum (ER), lipid droplet (LD), lysosome (Ly), and peroxisomes (Ps), primarily regulate the cellular functions including photoreceptor regeneration, autophagy and mitochondrial quality control [67]. Besides, the mitochondrial reactive oxygen species (ROS) affects both the composition and function of microorganisms. In some neurodegenerative diseases like Parkinson's disease, high levels of mitochondrial ROS can cause gut dysbiosis, which further exacerbates the disease progression [68]. Recent studies show that microbiota-mitochondrial degeneration affects the metabolic activities, disrupts neuroimmune homeostasis, and ultimately drive pathological alterations in key retinal structures during early AMD [63]. In photoreceptors, mitochondrial dysfunction significantly compromises

ATP generation, resulting in outer segment degeneration and diminished phototransduction efficiency. The phagocytic activity of RPE cells is also impaired, leading to lipofuscin accumulation. Bruch's membrane exhibits progressive deposition of lipids and proteoglycans, leading to the formation of basal laminar deposits and soft drusen. Choriocapillaris endothelial cells undergo fenestration loss, contributing to reduced choroidal perfusion and ischemia. Activated microglia accumulate near Bruch's membrane, exacerbating inflammatory responses through purinergic signaling pathways [63] (Fig. 3D). These interconnected pathological alterations underscore the pivotal role of microbiota-mitochondria axis dysregulation in the initiation and progression of AMD.

3.4 Microbiota-directed therapeutic target for age-related macular degeneration

Gut dysbiosis contributes to the progression of AMD through sustaining inflammatory responses, activating complement cascade, and disrupting microbiota-mitochondria axis [55, 60, 63]. Empirical studies confirm that modulating the gut-retina axis with interventions such as the heat-killed probiotic *Lactobacillus paracasei* KW3110, microbial BAs metabolites (TUDCA and UDCA), UAs, zinc supplementation, and dietary omega-3 long-chain polyunsaturated fatty acids (LCPUFAs) can attenuate retinal inflammation, reduce photoreceptor loss, and suppress pathological angiogenesis. These findings support the therapeutic potentials of targeting the gut microbiota in AMD [69-73]. A detailed synthesis of these microbiota-based interventions is provided in Section 10.

4. Gut microbiota and diabetic retinopathy

4.1 Microbiological characteristics of diabetic retinopathy

DR, a prevalent microvascular manifestation of diabetic mellitus (DM), has also been closely associated with aging-related processes [74]. Advanced age is independently linked to the development and advancement of DR, primarily attributable to the cumulative effects of oxidative stress, and age-related metabolic dysregulation [74-76]. Typically, DR can be categorically into the non-proliferative and proliferative forms according to the presence or absence of neovascularization. Non-proliferative diabetic retinopathy (NPDR) represents the initial phase of the disease, during which the manifestations may be mild or nonexistent. At this stage, the vascular architecture of the retina becomes compromised. Microaneurysms, tiny bulges within the blood vessels, have the tendency to

hemorrhage fluid into the neuro-retina, which can result in macular edema. Proliferative diabetic retinopathy (PDR) represents the more advanced stage of the condition. At this stage, the microvascular damage and circulatory problems lead to insufficient blood supply and retinal hypoxia. The retina afflicted to the growth of neovascular, which has potential to hemorrhage [77]. The senescence of retinal cells, particularly pericytes and endothelial cells, may significantly exacerbate microvascular damage in diabetic patients, thereby accelerating the progression from NPDR to PDR [78]. Emerging evidence suggests that gut microbiota can affect glucose metabolism, insulin resistance, and the secretion of enteric insulin [79]. In this context, researchers propose that gut dysbiosis may serve as a contributing factor to DR. For instance, clinical cohort studies involving patients with DM and DR have revealed gut dysbiosis at both phylum and genus levels. Compared with healthy controls (HC), the microbiota in human patients with both DM and DR shows a decline in anti-inflammatory, probiotic and some potentially pathogenic bacteria. In particular, this change is more remarkable in patients with DR [80]. In these clinical cohorts, the dominant phyla within the microbiota consist of Firmicutes, Actinobacteria, Bacteroidetes, and Proteobacteria. The alpha diversity reveals a substantial difference in the gut microbiota composition between HC and Type 2 diabetes mellitus (T2DM). Further analysis in human subjects indicates that two prominent phyla, Actinobacteria and Bacteroidetes, are significantly reduced in patients with DR compared with HC [80]. Another clinical cohort study has shown that the proportion of Bacteroidetes to Firmicutes increases in DR patients compared with these simple DM patients, indicating a potential biomarker for the advancement of DR in individuals suffering from T2DM [81]. Thus, in clinical settings, the gut microbiota of the DR patients exhibits distinct characteristics at the phylum level when compared with both the HC and patients with T2DM singularly [80]. On the other hand, clinical observations indicate that DM patients without DR exhibit significantly higher levels of Pasteurellaceae than those with DR, suggesting that Pasteurellaceae may serve as a rational biomarker for differentiating the occurrence of DR in DM [34]. Besides, comparative clinical data demonstrate a significant reduction in the abundance of 10 genera in T2DM patients and 20 genera in DR patients compared with HC. DR patients exhibit elevated levels of pro-inflammatory bacteria (Shigella) and reduced populations of the beneficial genera (Bifidobacterium and Lactobacillus) [80]. Accordingly, these clinical findings support the inference that the exacerbated inflammatory response in DR is closely associated with the diminished abundance of anti-inflammatory bacteria.

4.2 Regulatory mechanisms underlying the gut-retina axis

4.2.1 Gut microbiota metabolites mediated effects on diabetic retinopathy

LPS is a MAMP characterized by its lipid A-based glycolipid structure. It functions as a pro-inflammatory factor that can induce insulin resistance [30, 82]. It has been found that the levels of Bacteroidetes and Desulfo bacterota, two gram-negative bacteria capable of synthesizing LPS, increase substantially in DR patients compared with those afflicted with DM singularly [83]. Upon lysis or injury to the bacteria, the LPS is released into the gut and subsequently translocating into the bloodstream and elicits the endotoxemia [82]. Critically, LPS can infiltrate the circulatory system via direct diffusion due to the increased intestinal permeability in DR patients [30]. Subsequently, LPS is transported to peripheral tissue through lipoprotein-mediated mechanisms, predominantly via chylomicrons, where it interacts with the membrane-bound CD14 (mCD14) and TLR4 receptor complex on innate immune cells. This binding event can activate the NF- κ B signaling pathway and expression of pro-inflammatory cytokines, including TNF- α (Fig. 2). The elevated TNF- α levels then induce aberrant serine residue phosphorylation in insulin receptor substrate-1 (IRS-1), culminating in the development of insulin resistance [30, 84]. Beyond this systemic effect, circulating LPS of gut origin can directly contribute to retinal pathology in diabetes. LPS can promote the expression of adhesion molecules like ICAM-1 on retinal endothelial cells (RECs), thus promoting leukostasis and capillary occlusion (Fig. 2). This pathological process leads to retinal ischemia and subsequent neovascularization in PDR [40]. Concurrently, experimental evidence has confirmed that LPS can directly activate retinal microglia (Fig. 2). This microglia-mediated neuroinflammation exacerbates neuronal damage, highlighting a dual pathogenic role for LPS in both the vascular and neurodegenerative components of DR [40].

SCFAs, including butyrate, acetate, and succinate, are the key fermentation products of dietary fibers, commonly referred to as “resistant starch.” These SCFAs bind to GPCRs including the FFAR2/FFAR3 [30]. They offer a multitude of advantages in the realms of energy metabolism, maintenance of gut homeostasis, and immune response regulation [30]. These compounds have the capacity to suppress inflammatory reactions and oxidative stress, while also functioning as a signaling molecule that influences glycolipid metabolism between gut microbiota and the host organism [30]. Acetate and butyrate are capable of selectively activating intestinal L-

cells, thereby enhancing the secretion of GLP-1 and the PYY. It has been shown that GLP-1 can reduce retinal cell apoptosis and autophagy by reducing the expressions of NADPH oxidase 3 (NOX3), SOD2, caspase-3, and light chain 3B (LC3B), while concurrently enhancing the expression of B-cell lymphoma 2 (Bcl2) in the retina of Type 2 diabetic mice [85]. However, the diminished presence of butyrate-generating bacteria in DR patients mitigates SCFAs levels and inhibits the secretion of GLP-1 [80]. In this context, researchers propose that the reduced SCFAs levels and the development of IR may represent a potential pathogenic mechanism of DR [86]. TMAO, a metabolite derived from the gut microbiota, is predominantly synthesized by dietary L-carnitine, choline, and trimethylamine (TMA). The gut microbiota converts L-carnitine and choline into TMA, which is then oxidized by flavin dependent monooxygenase 3 (FMO3) to form TMAO in the liver [87]. A recent study shows that elevated concentrations of TMAO can compromise glucose homeostasis, and results in an adverse prognosis in diabetic patients. Clinical data reveals a definite correlation between the TMAO levels and the severity of diabetic complications [88]. Apart from its established role in exacerbating insulin resistance and dyslipidemia, TMAO exerts detrimental effect on the vascular endothelium [87]. More profoundly, TMAO inflicts direct damage to the vascular endothelium by promoting oxidative stress and activating specific inflammatory pathways [41]. Mechanistic studies have revealed that TMAO activates the NLRP3 inflammasome via the SIRT3-SOD2-mtROS axis [41] (Fig. 2). This cascade triggers retinal inflammation and injury, a key driver of DR progression [41]. Given its central role in these pathogenic pathways, plasma TMAO may act as a promising biomarker for DR risk stratification. Future large-scale prospective studies are warranted to validate its diagnostic utility and explore its potential as a target for therapeutic intervention.

4.2.2 Kynurenine Pathway Metabolites in Diabetic Retinopathy

Kynurenines (KYNs) are tryptophan-derived metabolites produced via the kynurenine pathway, whose first step is controlled by the rate-limiting enzyme indoleamine 2,3-dioxygenase (IDO) [89]. A key upstream regulator of this pathway is the gut microbiota. Specifically, gut dysbiosis can disrupt immune homeostasis and promote a chronic inflammatory state, leading to the upregulation of IFN- γ , which acts as a potent inducer of IDO expression [90-91]. The clinical significance of this pathway in DR is underscored by the finding that patients with NPDR exhibit significant elevations in IDO mRNA and serum levels of KYN, kynurenic acid (KYNA), and 3-

hydroxykynurenine (3-HKYN). This elevation escalates further in the PDR stage [92]. Within this metabolic cascade, KYN is further metabolized into both KYNA, a compound with established pro-oxidant properties, and 3-HKYN [91, 93]. Critically, 3-HKYN can auto-oxidize under conditions of antioxidant depletion (glutathione deficiency), directly generating hydrogen peroxide [91]. This IDO-driven production of hydrogen peroxide provides a sustained endogenous source of ROS, contributing to oxidative damage on retinal cells and promoting microvascular dysfunction. Consequently, the activation of IDO, primed by gut dysbiosis and inflammation, leads to the accumulation of pro-oxidant metabolites [91]. This process constitutes a key mechanism by which the kynurenine pathway accelerates the pathological process of DR.

4.2.3 Stimulator of interferon genes in inflammation response

The gut-retina axis represents a burgeoning concept describing a tight interaction between the gut host-microbiota interface and the retina. Stimulator of interferon genes (STING), a ubiquitously expressed adaptor protein in the ER is activated by the cytosolic DNA sensor cyclic GMP-AMP synthase (cGAS). This activation will facilitate the activation of the transcription factors interferon regulatory factor 3 (IRF3) and NF- κ B, leading to downstream effects such as inflammatory response, autophagic flux, and programmed cell death [94]. A snowballing effect involving gut dysbiosis and the abnormal activation of the intestinal STING pathway has been identified recently. Gut dysbiosis prompts the release of microbial DNA from certain bacteria, with cyclic dinucleotides (CDNs) being prime examples. CDNs trigger K63-linked ubiquitination of STING in intestinal myeloid cells, and lead to its abnormal accumulation [95]. STING then causes the death of intestinal epithelial cells, thereby deteriorating the gut barrier function and exacerbating dysbiosis. On this basis, microbes and their products can enter the bloodstream as the gut barrier weakens. These substances further activate the cGAS-STING pathway in the gut, triggering inflammatory and innate immune responses, thereby completing the positive feedback loop [96] (Fig. 4). Through these mechanisms, these bacterial products derived from the gut gain access to the retinal tissue. They cause mitochondrial dysfunction and initiate the release of self-DNA within the retinal cell [97]. The self-DNA is capable of activating the cGAS-STING signaling pathways in various retinal cell types, including RPE, retinal microvascular endothelial cell (RMEC), microglia, and retinal ganglion cells (RGCs). It is noteworthy that the STING can also be triggered by CDNs or endoplasmic

reticulum stress (ERS) via a DNA-independent manner. These activations of this cascade finally contribute to retinopathy through the gut-retina axis [96].

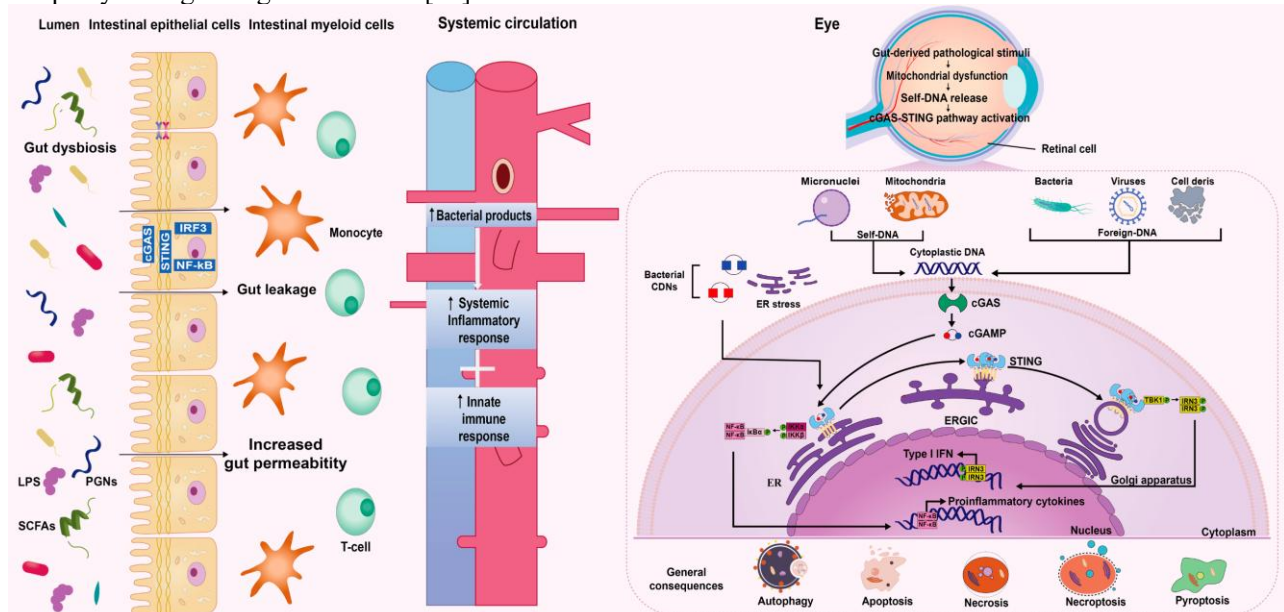


Figure 4. The STING pathway in the gut-retina axis. Intestinal STING accumulation promotes gut leakage, allowing microbial products to enter systemic circulation and trigger innate immune responses. In the retina, cytoplasmic DNA activates the cGAS-STING pathway, inducing type I interferons and inflammatory cytokines. STING can also be activated by bacterial cyclic dinucleotides or ER stress. This leads to autophagy, various forms of cell death, and inflammation, contributing to diabetic retinopathy and other retinal diseases. **Note.** cGAMP, cyclic GMP-AMP; ERGIC, ER–Golgi intermediate compartment; IFN, interferon; IRF3, interferon regulatory factor 3; TBK1, Tumor necrosis factor receptor-associated factor family member associated NF- κ B activator-binding kinase 1.

4.2.4 Gut-retina axis regulates diabetic retinopathy via angiotensin-converting enzyme 2

Angiotensin-converting enzyme 2 (ACE2) is emerging as a central regulator of the gut-retina axis in the pathogenesis of DR [98]. ACE2 deficiency in diabetic mice disrupts the gut vascular barrier (GVB). This defect is caused by a specific reduction in bone marrow-derived myeloid angiogenic cells (MACs) within the intestinal parenchyma, without a corresponding increase in inflammatory monocytes, thus suggesting an impairment of intrinsic repair mechanisms [43]. Concurrently, this deficiency reshapes the gut microbiota, leading to an enrichment of bacteria such as *Bifidobacterium animalis* that overexpress genes related to PGNs biosynthesis [43]. The compromised barrier integrity facilitates the translocation of PGNs into the systemic circulation. Consequently, PGNs-induced internalization of endothelial junction proteins compromises the retinal vascular barrier, thereby increasing vascular permeability and exacerbating DR [43] (Fig. 2).

4.2.5 Vascular Endothelial Growth Factor in diabetic retinopathy

Accumulating evidence suggests the gut microbiota and its metabolites act as pivotal regulators of intestinal lymphatic vascular integrity [39]. The pivotal mechanism is the PRR-mediated recognition of commensal gram-positive bacteria by intestinal macrophages, which directly upregulate VEGF-C [39] (Fig. 2). The VEGF-C secreted by these macrophages serves as a critical maintenance factor for the adjacent lacteals, ensuring the structural integrity of these lymphatic capillaries and their function in dietary lipid absorption. Experimentally, depletion of vancomycin-sensitive gram-positive bacteria impairs this microbial recognition, suppressing VEGF-C secretion and disrupting the VEGF-C/VEGFR3 (vascular endothelial growth factor receptor 3) signaling axis in lacteals. This process ultimately leads to lacteal regression [39, 99–100]. The resulted gut barrier dysfunction may promote bacterial product translocation into circulation, potentially initiating chronic systemic inflammation [39, 84]. This inflammatory state, characterized by elevated cytokines such as IL-1 β and IL-6, constitutes a major driver of VEGF-A upregulation [101]. Given the pathogenic role of VEGF-A in mediating both aberrant vessel growth and vascular leakage in DR, these findings position the gut microbiota as a potential modulator of pathological processes in the retinal vasculature [101].

4.3 Microbiota therapy for diabetic retinopathy

Gut microbiota modulation represents a promising therapeutic strategy for DR, with both probiotics and postbiotics demonstrating their potentials to ameliorate retinal pathology [102-103]. Other effective approaches include chronic intermittent fasting (IF), which can remold gut microbiota and improve metabolic functions [104], as well as sodium butyrate supplementation which can restore intestinal barrier function and suppress inflammation. UAs further ameliorates retinal degeneration by activating cytoprotective pathways [105-106]. A systematic evaluation of these gut-targeted therapeutic strategies is consolidated in Section 10.

5. Gut microbiota and glaucoma

Glaucoma is an irreversible blindness disease that is characterized by the progressive degeneration of the optic nerve atrophy and visual field loss [107]. The RGCs are located in the inner retina and their axons extending to form the optic nerve. The degeneration of RGCs leads to optic disc cupping, a distinctive feature of visual impairment [108]. The etiology of RGCs loss in glaucoma is multifactorial, encompassing factors such as increased intraocular pressure (IOP), advanced age, hypoxia, neuronal overactivation, oxidative damage, and impaired mitochondrial function [108]. Advanced age is a major risk factor for the occurrence and progression of glaucoma, with a significant increase in prevalence among individuals over 60 years [109]. Age-related changes such as reduced trabecular meshwork cellularity, decreased aqueous humor outflow, and accumulation of extracellular matrix material can collectively contribute to the elevated IOP [109]. Nevertheless, a comprehensive understanding of glaucoma pathogenesis remains elusive owing to its chronic progression [108, 110]. The primary factor contributing to tissue damage in glaucoma is elevated IOP, and clinical practice has demonstrated that lowering IOP acts as an effective therapeutic modality. The condition has been categorized into two extensive types: open-angle glaucoma (OAG) and angle-closure glaucoma (ACG) [108]. As a neurodegenerative disease in the ocular system, glaucoma exhibits many similar characteristics with central nervous system diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS) [111]. Accumulating evidence suggests that Hp infection has the potential to influence the IOP of the host [112]. Pioneering researchers have utilized the anti-Hp IgG titer as an indicator to assess the correlation between Hp infection and glaucoma. They found that Hp-specific antibodies are significantly elevated in both serum and aqueous humor among patients with primary open-angle glaucoma

(POAG). The levels of titers for anti-Hp antibodies are positively correlated with the severity of glaucoma, as the titers of anti-Hp IgG antibodies are associated with the grade of vertical cupping [113]. A meta-analysis has also verified a significant correlation between Hp infection and the occurrence of glaucoma, with the active state of infection exhibiting the most pronounced association with the development of glaucoma [112]. Intriguingly, gut metabolites can exert beneficial influence on IOP. Hydrogen sulfide, an intestinal metabolite, has been demonstrated to decrease IOP in glaucomatous rabbits and protect retinal function. Mechanism study shows that hydrogen sulfide can impede the function of excitatory amino acid neurotransmitters and enhance the outflow of aqueous humor [114]. Some researchers have also found that butyrate is capable of reducing the IOP in normotensive rat model. However, this effect is absent in hypertensive rat model, and this process is independent of ocular sympathetic innervation [115].

5.1 Microbial-related pathogenesis of glaucoma

5.1.1 Helicobacter pylori infection can increase the intraocular pressure

From a pathogenic perspective, potential connections between Hp infection and glaucoma may encompass dysbiosis within the gastrointestinal microbiota and the subsequent release of inflammatory cytokines. Chronic Hp infection coupled with gastric inflammation could potentially induce the production of inducible nitric oxide synthase (iNOS), leading to the release of nitric oxide (NO) and the formation of reactive nitrogen species (RNS), including peroxynitrite, nitrogen dioxide (NO₂), and hydroxylamine (NH₂OH) [116]. The structural attributes of these molecules may facilitate systematic diffusion and elicit distal effects on the eye. Disruption of the BRB by Hp infection makes the ocular environment susceptible to RNS and nitrosative stress, culminating in mitochondrial damage through parthanatos (an iterative DNA fragmentation cascade), RGCs apoptosis and optic nerve atrophy [117]. The secretion of toxic autoantibodies, induced by molecular mimicry and anti-Hp IgG antibodies, as well as direct ocular contamination by Hp via the oral-nasal-olfactory pathway, may potentially contribute to the development of glaucoma [118]. More importantly, a recent study shows that Hp-induced gastritis may trigger fluctuations in the NO concentration, potentially altering its vasoactive activity and leading to instabilities in ocular arterial perfusion pressure. These disturbances cause transient ischemia-reperfusion injuries, and the elevations in IOP (Fig. 5A). However, microbial-related pathogenesis of glaucoma

requires further empirical verification through clinical studies [117].

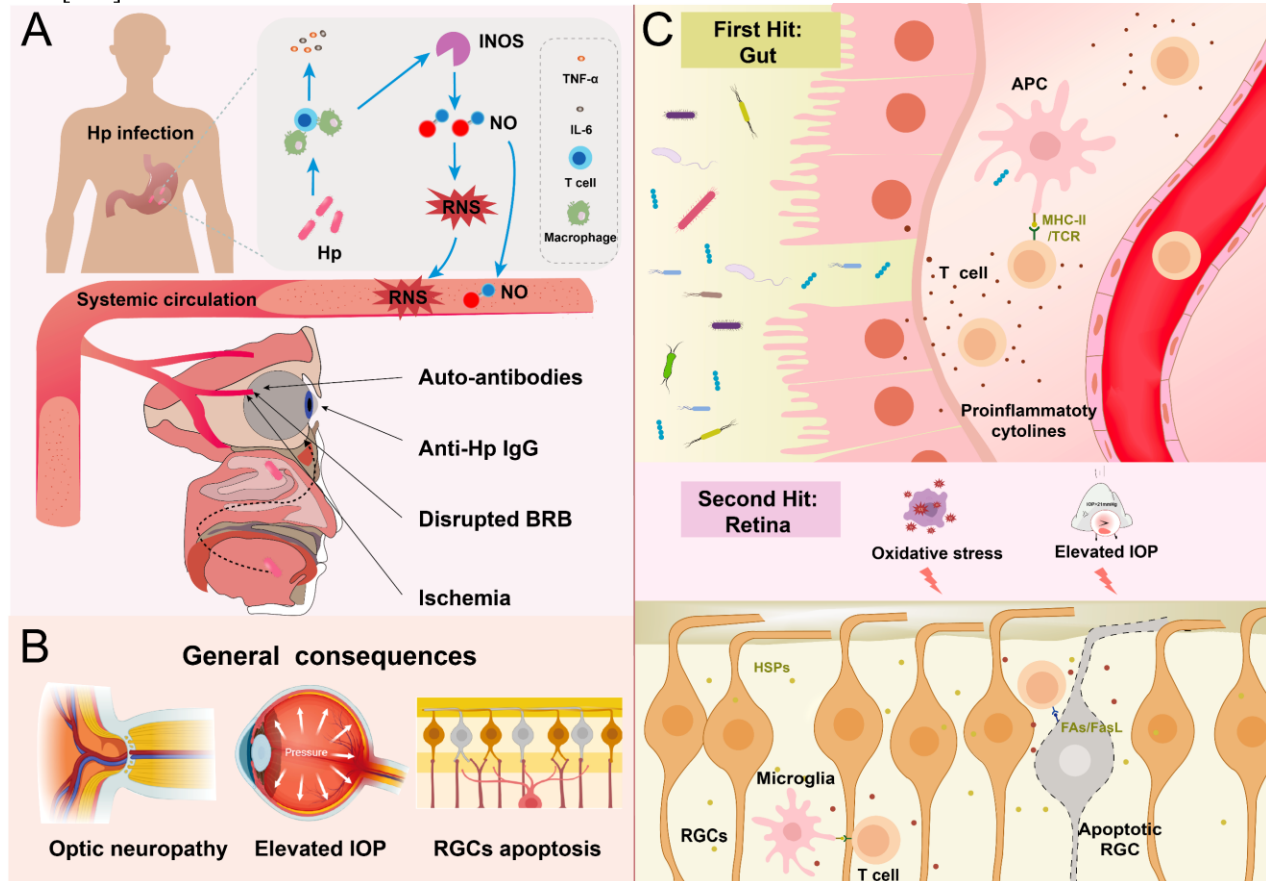


Figure 5. The microbiota-related pathogenesis of glaucoma. (A) Hp infection triggers systemic inflammation and releases mediators (TNF- α , NO) that compromise the blood-retinal barrier. Autoantibodies and ischemia further contribute to glaucoma development. (B) Key consequences include optic neuropathy, elevated IOP, and RGC apoptosis. (C) The “dual-hit” hypothesis: Gut dysbiosis permits autoreactive T cells primed by microbial antigens to enter circulation (first hit). These cells cross the compromised BRB and target RGCs expressing heat shock proteins, promoting apoptosis via Fas/Fas-L pathways and accelerating neurodegeneration (second hit). **Note.** APCs, antigen-presenting cells.

5.1.2 Bacteria-primed T cells induce autoimmunity in glaucoma

Immune-mediated attack on the neural retina is recognized as a contributing risk factor to glaucoma [119]. Once autoreactive CD4⁺ T cells are primed by the commensal microbiota, a transient increase in IOP can trigger their migration into the retina. These T cells recognize and react to heat shock proteins (HSPs), such as HSP27 and HSP60, which serve as potential antigens upregulating in RGCs under stress conditions. This recognition initiates an immune response that exacerbates retinal neurodegeneration [120]. Interestingly, it has been found that the gut microbiota serves as a predominant source of bacterial HSPs in humans [121]. The gut microbiota can produce bacterial HSPs that cross-react with human HSPs, thereby priming the immune system to attack RGCs under conditions of elevated IOP [120]. On

this basis, scholars have proposed the “dual-hit theory” to elucidate the correlation between the activation of T cells peripherally and gut dysbiosis in the pathogenesis of glaucoma. Initially, the augmented permeability of the gut leads to the formation of autoreactive T cells, which are primed by microbial HSPs. These autoreactive T cells subsequently enter the systemic circulation and migrate to the retina, leading to the apoptosis of RGCs (first hit). Ultimately, these autoreactive T cells breach the damaged BRB and become reactivated in the retinal parenchyma (second hit) [119, 122]. After immunization with HSP27 or HSP60, pre-sensitized T cells are also capable of eliciting RGCs apoptosis through promoting the production of Fas-ligand and the expression of its corresponding receptor on the RGCs [123] (Fig. 5C). Given the pivotal role of T cell-mediated autoimmunity in glaucoma pathogenesis, researchers have extensively investigated immune-modulatory therapies targeting

these pathways. In particular, copolymer-1 (COP-1), a synthetic peptide that mimics myelin basic protein, has demonstrated potential in redirecting pathogenic T cells away from cross-reactive retinal antigens, consequently alleviating neurodegeneration [119]. Taken together, these findings suggest that glaucoma can be caused by CD4⁺ T cells activated by bacteria, which infiltrate the eyes due to the compromised BRB, and subsequently induce neurodegeneration through cross-reacting with these RGCs expressing HSPs [124].

5.2 Therapeutic interventions targeting the gut microbiota

Gut microbiota modulation emerges as a viable management strategy for glaucoma. Preclinical studies have confirmed that fermented maize slurry and its supernatant can protect RGCs via microbiota alteration, while clinical evidence supports Hp eradication can lower IOP and preserve visual fields [35, 125]. The mediterranean-DASH intervention for neurodegenerative delay (MIND) diet decreases independently the glaucoma risk, and FMT demonstrates neuroprotective efficacy in glaucomatous murine experimental models [36, 126]. A comprehensive analysis of these therapeutic approaches is presented in Section 10.

6. Gut microbiota and uveitis

6.1 Pathogenesis of the uveitis

Uveitis is an overarching term that encompasses a spectrum of inflammatory disorders affecting the uveal, such as iris, ciliary body, and choroid. Uveitis acts as a prominent contributor to blindness in developed nations, with estimates suggesting it accounts for 10%-15% of severe visual impairments [127]. Aging is associated with these chronic and severe forms of uveitis in humans, probably due to immune senescence and cumulative tissue damage [128]. Typically, uveitis is anatomically subdivided into anterior, intermediate, and posterior forms, depending on which ocular segment is primarily affected. Besides, uveitis can be categorized into two primary groups based on its etiology: infectious and non-infectious uveitis. The latter is the most prevalent type and is often linked to systemic inflammatory conditions including systemic sarcoidosis, Behcet's disease, and Vogt-Koyanagi-Harada syndrome [129-130]. Recent single-cell studies in murine models demonstrate that aging alters immune cell composition, reduces naive T cells while expanding effector subsets, and ameliorates experimental autoimmune uveitis (EAU) by impairing Th17 cell pathogenicity through downregulating the IL-23 receptor/granulocyte-macrophage colony-stimulating

factor (IL-23R/GM-CSF) axis [128]. The murine models of experimental uveitis initially provide empirical support for the autoimmune hypothesis of non-infectious uveitis [131]. However, these models fail to replicate the complete phenotypic spectrum of human non-infectious uveitis [132]. Fundamental disparities in genetic makeup, dietary intake, and indigenous microbiota, raise questions regarding the capacity of murine uveitis models to accurately recapitulate the salient characteristics of the corresponding human pathology [133]. Interestingly, recent revelations on the role of commensal microbiota have substantially altered our comprehension of ocular pathologies [134]. The interaction between the host and its microbiota has become a pivotal element in elucidating the mechanisms underlying immune responses and immunological pathologies like uveitis.

6.2 T cells are activated by gut microbiota in autoimmune uveitis

Autoimmune uveitis is a visually compromising condition that arises without an identifiable infectious etiology [135]. The precise location and mechanism by which autoreactive T cells are primed to cause disease within an anatomically immune-privileged site, remains elusive [135]. Recent investigations into the experimental uveitis model have elucidated the important role of gut microbiota in the induction of autoreactive T cells and ocular inflammation [136]. These findings have postulated an innovative hypothesis that the activation of pathogenic autoreactive T helper cells is initiated by pathogenic gut microbial strains [137]. In the R161H murine model of uveitis, retina-specific T cells within the gut lamina propria preferentially differentiate Th17 cells under the microbiota-derived signaling pathway, antedating the clinical manifestation of the disorder in the ocular tissue [138]. In fact, the depletion of commensal microbiota mitigates uveitis and inhibits the activation of Th17 cells in the intestinal tract. In particular, the activation of retina-specific T cells is entirely unrelated to endogenous antigens (such as interphotoreceptor retinoid binding protein, IRBP). Alternatively, it requires signaling via the clonotypic autoreactive T cell receptor (TCR) in response to microbiota-dependent stimuli. Activated Th17 cells can infiltrate the ocular environment, inducing an inflammatory response that leads to ocular tissue damage and the development of autoimmune uveitis (Fig. 6). These findings point to a previously unidentified mechanism in which the interaction of specific TCR with non-cognate stimuli within the gastrointestinal tract elicits the activation of autoreactive T cells, in autoimmune disorders [136].

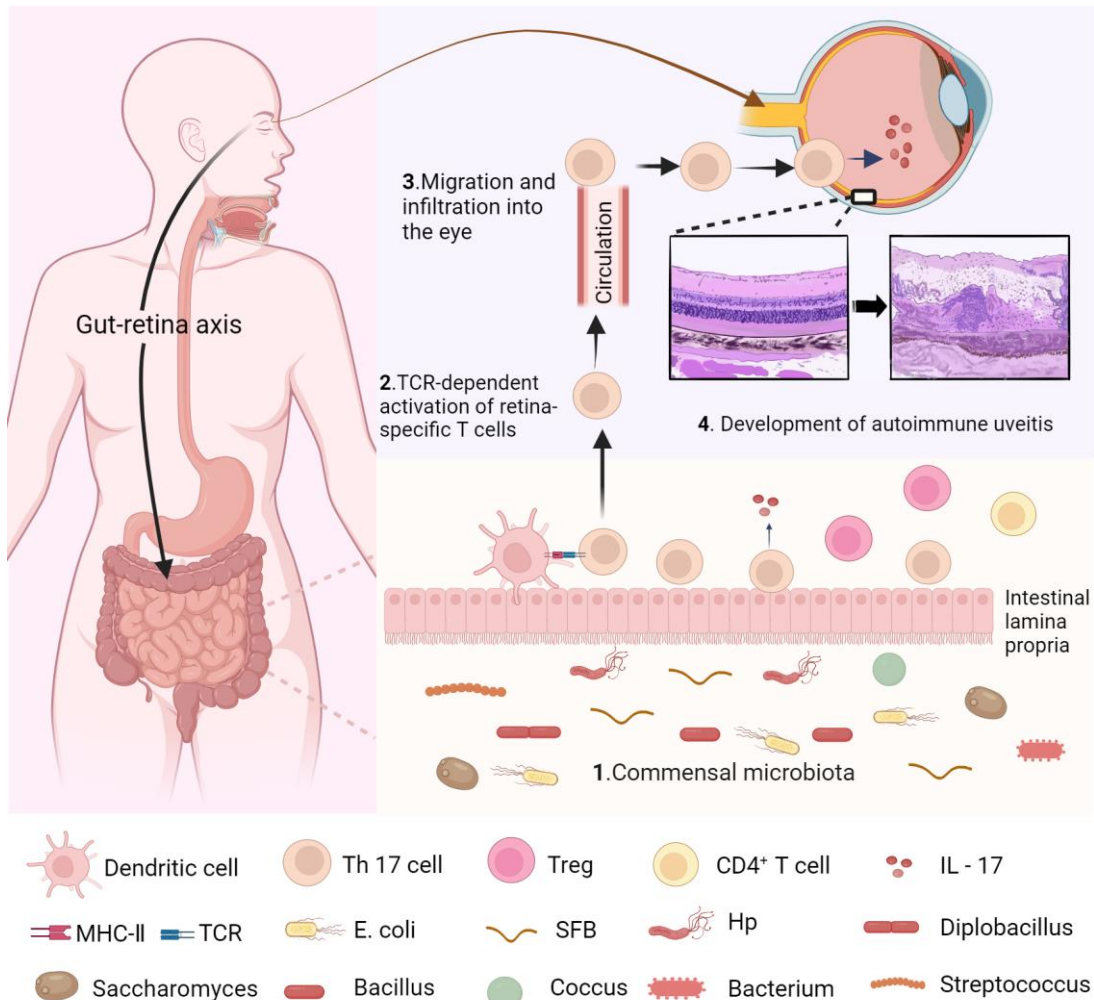


Figure 6. The gut-retina axis in autoimmune uveitis pathogenesis. In intestinal lamina propria, retinal-specific T cells activate in response to microbiota-derived stimulatory signals (via TCR). They then preferentially differentiate into Th17 cells (unaffected by endogenous retinal antigens). Activated Th17 cells migrate to the eye, releasing cytokines like IL - 17 to trigger an inflammatory cascade, causing ocular tissue damage, autoimmune uveitis, and vision loss.

6.3 Associations between gut dysbiosis and HLA-B27-associated uveitis

HLA-B27, an important MHC class I molecule, is fundamental to self-identification and antigenic presentation, and has been implicated in a multitude of immune-mediated pathologies [132]. Studies have indicated that HLA-B27 is intimately associated with a cluster of arthritic conditions sharing analogous clinical characteristics, as well as an inflammatory ocular disorder affecting the iris and ciliary body, termed acute anterior uveitis (AAU) [133]. Some researchers have proposed that gut microbiota is a key driver in the pathogenesis of HLA-B27-associated disease [135]. It has been discovered that the presence of *Prevotella vulgatus* and *Akkermansia muciniphila* is correlated with HLA-B27 transgenic rats, in conjunction with alterations in the

levels of Actinobacteria and Prevotellaceae in individuals afflicted with HLA-B27-related disorders [137]. The alteration of the intestinal metabolome in HLA-B27 transgenic rats encompasses a reduction in medium-chain fatty acids, an elevation in mucus metabolites (attributable to *A. muciniphila*), a diminished level of secondary bile acids, as well as modifications in the metabolism of tryptophan. In particular, a pronounced elevation in N-acetylmuramate, a pivotal component of bacterial cell walls, is detected in the antecedent phase of this disease [139]. Nevertheless, emerging research has unveiled significant discrepancies between the gut microbiota profiles observed in HLA-B27 transgenic rats and those identified in human AAU patients. While rodent models exhibit characteristic microbiota, such as the enrichment of *Prevotella* and *Akkermansia*, clinical studies of AAU patients have reported distinct dysbiosis patterns.

Specifically, these patterns include elevated *Veillonella* abundance correlated with systemic inflammatory markers like C-reactive protein (CRP), along with altered metabolic profiles characterized by increased shikimic acid levels. These interspecies variations may arise from fundamental differences in disease phenotypes, such as spondyloarthritis in rodents versus ocular inflammation in humans [139]. Another sole peer-reviewed microbiome study in AAU identifies significant β -diversity differences between patients and healthy controls through unweighted UniFrac analysis, although the specific microbial shifts diverge from the findings in transgenic rats [140]. This discordance highlights the necessity for integrated multi-omics approaches to uncover conserved functional disturbances, such as metabolic pathway dysregulation, that may transcend taxonomic variations.

7. Gut microbiota and retinitis pigmentosa

7.1 Neuroinflammation in retinitis pigmentosa

Retinitis pigmentosa (RP) constitutes a diverse category of inherited disorders characterized by the degeneration of photoreceptors, which ultimately results in complete loss of visual acuity [141]. The death of photoreceptors is concurrent with augmented prevalence of microglia activation and visual pathway remodeling [142]. Characteristic clinical presentations of RP include the pigmentation of bone spicules, the attenuation of retinal vasculature, and the waxen pallor of the optic disc [143]. It has been established that over 80 unique genes are implicated in the mutations causatively associated with RP [144]. Despite mutations continuing to be the principal cause of RP, evidence accumulated over the past several decades has delineated that neuroinflammation plays a pivotal role in the advancement of the disease [145]. The neuroinflammation process is activated by the innate immune system, encompassing dysregulation of the immune barrier, the activation and infiltration of immune cells, as well as the heightened expression of both local and systemic inflammatory mediators in the patients of RP [146-147]. Aging critically exacerbates RP progression by amplifying neuroinflammatory processes. Age-related alterations in the retinal microenvironment disrupt immune homeostasis and promote pathological microglial activation. Senescent microglia exhibit decreased motility, reduced arborization, and impaired responsiveness to signaling molecules such as ATP, thereby compromising their immune surveillance and phagocytic functions [148]. Conversely, the genetic depletion or the pharmacological inhibition of microglial phagocytosis has been shown to mitigate the progression of photoreceptor apoptosis in murine models of RP [147]. Intriguingly, the microbial landscape and functional

capacity of the microbiota are inherently modulated by the innate immune system. In this context, gut dysbiosis has the potential to elicit immune system dysregulation, thereby precipitating in the pathogenesis of RP [149].

7.2 Gut microbiota shifts in retinitis pigmentosa

Researchers have conducted comprehensive investigations to verify changes of gut microbiota linked to RP [142]. In the rd10 murine model, the retinal responses to light flashes and visual acuity are compromised when compared with those parameters in age-matched control mice. The 16S rRNA gene amplicon sequencing data demonstrates marked dysbiosis of the gut microbiota in the rd10 murine model, as evidenced by distinct discrepancies in both alpha and beta diversity at the genus, species, and amplicon sequence variant (ASV) levels. In particular, four prevalent ASVs, namely *Rikenella* spp., *Muribaculaceae* spp., *Prevotellaceae* UCG-001 spp., and *Bacilli* spp., which are commonly found in the healthy gut microbiota, are absent in the intestinal flora of rd10 mice. Conversely, a marked enrichment of *Bacteroides caecimuris* is detected in rd10 mice. These findings underscore a definite correlation between the pathogenesis of RP and corresponding alterations in the gut microbiota [142]. Accumulating evidence suggests that gut microbiota functions as a modifier of retinal inflammatory response via the exchange of intestinal microbiota. This is exemplified by studies showing that FMT from young to aged mice reverses age-related retinal inflammation, restores proteins like RPE65, and reduces C3 deposition. Conversely, transferring aged microbiota to young mice accelerates these detrimental changes [9] (Fig. 7A). These findings highlight the bidirectional communication between the gut and retina, where microbial composition directly influences retinal health through the gut-retina axis.

7.3 Gut-retina axis link to retinitis pigmentosa

An investigation using MERTK-mutated Royal College of Surgeons (RCS) rats has demonstrated that specific pathogen-free (SPF) rearing conditions exert protective effects against retinal degeneration [150]. Compared with conventionally housed counterparts, SPF-maintained rats exhibit reduced photoreceptor apoptosis and delayed disease progression. Microbiota profiling reveals distinct variations in the gut microbial communities among rats, characterized by the enrichment of Proteobacteria and Spirochaetes while decreasing Actinobacteria and Bacteroidetes abundance in SPF environment. Lower relative abundances of *Prevotella copri* (ASV03122) and *Ruminococcaceae Oscillospira* (ASV12750) are strongly

associated with exacerbated retinal damage, as measured by fundus autofluorescence imaging [150]. These findings establish a novel mechanistic link between environmental conditions, gut microbiota remodeling, and retinal neurodegeneration in RP. Recent studies utilizing the rd10 mouse model have revealed that short-term HFD accelerates retinal degeneration through a gut-retina axis [151]. HFD induces intestinal microbiota dysbiosis, characterized by elevated levels of proinflammatory bacteria, including *Bilophila* and *Lactococcus* species, alongside a reduced abundance of beneficial *Muribaculaceae*. This microbial imbalance triggers systemic inflammation and activates retinal

glycogen synthase kinase 3 beta (GSK3 β)/NF- κ B signaling pathways, contributing to increased expressions of IL-6 and IL-1 α . The microglial cells are activated as reflected in a twofold increase in cell density, and oxidative stress is aggravated, as demonstrated by elevation of 4-HNE levels. These combined effects ultimately lead to photoreceptor damage and subsequent visual function decline [152]. Taken together, this study bolsters the “gut-retina axis” notion in the context of RP pathogenesis. Although current research is in its incipient phase, the gut microbiota represents a prospective therapeutic method for the management of RP.

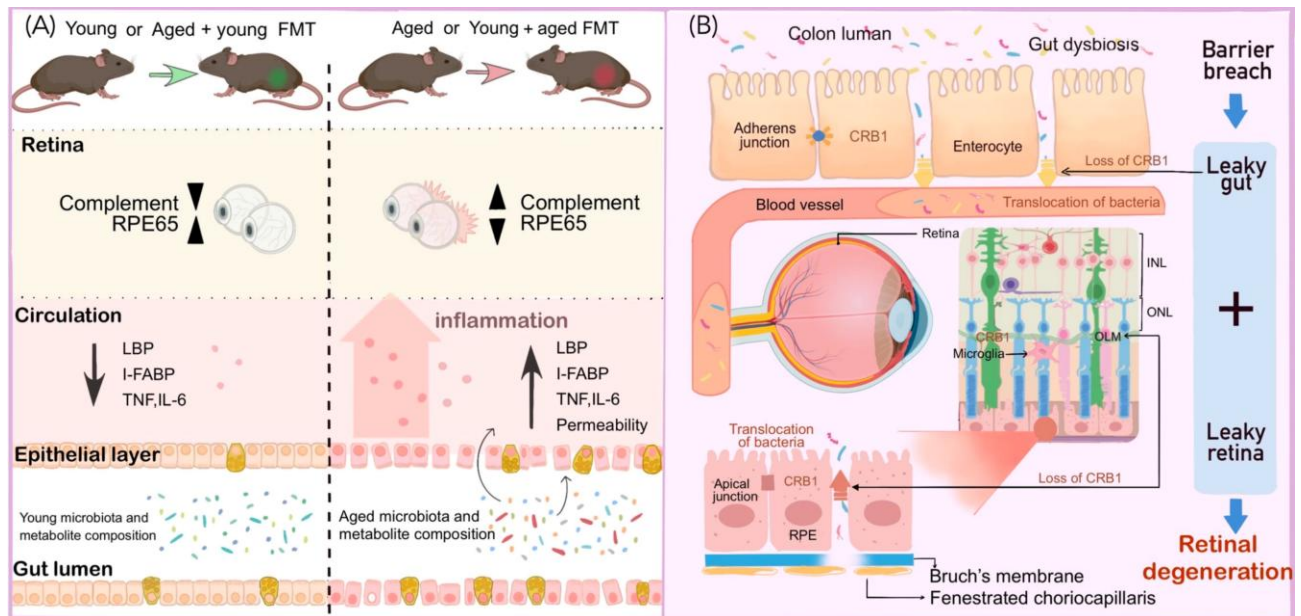


Figure 7. Gut microbiota interventions and CRB1 deficiency in retinal health. (A) Young microbiota transplantation (FMT) reduces retinal inflammation, restores RPE65, and improves gut barrier integrity, while aged FMT exacerbates complement deposition and compromises retinal and intestinal health. **(B)** CRB1 deficiency disrupts adherens junctions in both the gut and RPE, leading to bacterial translocation, barrier failure, and retinal degeneration. **Note.** INL, inner nuclear layer; ONL, outer nuclear layer; OLM, outer limiting membrane; LBP, lipopolysaccharide-binding protein; I-FABP, intestinal fatty acid-binding protein.

7.4 CRB1 is associated with bacteria translocation from gut

Physiologically, the expression of the CRB1 protein is found to be concentrated in the apical junctional complexes of RPE cells and colonic enterocytes [153]. Hence, the occurrence of CRB1 mutations can mitigate its protein expression at the respective locations [154]. It has been well-established that mutations in the CRB1 gene can initiate various phenotypes of retinal degeneration, including Leber congenital amaurosis and RP [155-156]. The rd8 mice model, is a widely utilized model in the investigation of CRB1-associated retinal degeneration [157]. Researchers aim to determine whether the augmented expression of antimicrobial genes in RP mouse lesions correlates with retinal microorganisms. To

this end, they conducted meta-transcriptomic analyses on retinal tissue from rd8 mice. They have verified that the compromised integrity of outer BRB and the colonic epithelial barrier can result in the translocation of intestinal bacteria, thereby triggering ocular inflammatory reactions (Fig. 7B). On the other hand, several interventions can effectively prevent the initiation and exacerbation of these retinal pathologies. These include deriving mice germ-free (GF), systemic administration of broad-spectrum antibiotics, or restoring functional CRB1 expression in the lower GI tract using an adeno-associated virus (AAV) 2 vector [154]. Therefore, the data indicates that retinal degeneration associated with CRB1 is contingent upon bacterial migration from the gastrointestinal tract. It is postulated that the utilization of

antimicrobial compounds may have the efficacy to mitigate these devastating retinopathies.

7.5 Microbiota-targeted nutrient interventions for retinitis pigmentosa

Nutritional interventions exert synergistic effects on RP by concurrently protecting retinal integrity and reshaping gut microbial ecology. Specific combinations such as chitosan with β -carotene and lutein with epigallocatechin-3-gallate (EGCG) can alleviate retinal degeneration while modulating gut microbiota composition and function. These findings validate the therapeutic relevance of the gut-retina axis in RP [158]. Systematic analysis of these nutrient-based approaches is presented in Section 10.

8. Gut microbiota and central serous chorioretinopathy

Central serous chorioretinopathy (CSC) is a retinopathy that characterized by serous retinal detachment, predominantly affecting the macula [159]. CSC ranks as the fourth most prevalent non-surgical retinopathy associated with fluid leakage, following AMD, DR and RVO (retinal vein occlusion) [160]. CSC is accompanied by pigment epithelial detachments (PEDs), RPE dysfunction, choroidal thickening, increased permeability, and venous congestion [161]. Most importantly, CSC demonstrates distinct clinical characteristics correlated with aging. Advancing age induces significant alterations in both the choroid and RPE, including a higher prevalence of bilateral macular abnormalities, multiple drusen, and multifocal leakage patterns. These age-related phenotypic changes are frequently observed in older populations with chronic and recurrent forms of the disease [162]. Conventionally, CSC has been arbitrarily classified into acute and chronic variants, contingent upon the persistence of subretinal fluid. Predominantly, instances of CSC manifest as an acute CSC, with the subretinal fluid resolving spontaneously within a timeframe of 3 to 6 months [160]. Chronic CSC is inherently characterized by its “chronicity,” accompanied by a higher degree of RPE disruption when contrasted with acute CSC. The persistence of subretinal fluid for durations exceeding six months in this chronic condition, which comprises approximately 5%-15% of all CSC occurrences. The majority of acute CSC cases resolve spontaneously, but few patients may evolve into the chronic variant. Even after the initial resolution of subretinal fluid, some patients may experience subsequent relapses in certain instances, which are termed recurrent CSC [163-164]. Interestingly, the international expert group recently proposed an innovative classification system, which

categorizes CSC into simple or complex types based on the results from multimodal imaging techniques [163].

8.1 Epidemiology study of the central serous chorioretinopathy

It is widely acknowledged that psychological stress constitutes a dominant risk factor for the CSC [165]. The utilization of exogenous corticosteroids is acknowledged as a definitive risk factor for CSC, and endogenous hypercortisolism is similarly implicated in the pathogenesis of CSC [166]. Researchers have also suggested that pregnancy, systemic hypertension, organ transplantation, sleep disturbances, and obstructive sleep apnea are additional risk factors associated with the development of CSC [167-170]. The genetic risk factors, such as the SNPs in CFH and ARMS2, which are concurrently implicated in the pathogenesis of AMD, may indeed contribute to the pathophysiology of CSC [161]. Additional SNPs encompass the nuclear receptor subfamily 3 group C member 29 (NR3C2) gene, cadherin 5 (CDH5) loci, vasoactive intestinal peptide receptor 2 (VIPR2) loci and solute carrier family 7 member 5 (SLC7A5), further underscoring the potential roles of dysregulated complement activation, vascular permeability, neuroendocrine signaling, and cellular metabolism in CSC development [171-174]. Contemporary research has shifted the focus towards the gut microbiota mediated effects on CSC. For instance, recent empirical evidence points to the potential correlation between Hp infection and the pathogenesis of CSC. It has been hypothesized that the underlying mechanism should be attributed to the Hp induced immune reactions in choroidal endothelial cells, which subsequently result in vascular abnormalities as a consequence of molecular mimicry [175]. Molecular mimicry occurs when antigens from pathogens (such as Hp) exhibit structural resemblances to host proteins, prompting an immune response that erroneously attacks the host's own tissue. In CSC, antibodies targeting Hp antigens, especially those produced against the cytotoxin-associated gene-A (CagA) protein and HSPs, may cross-react with similar proteins in choroidal endothelial cells. This immune cross-reactivity can induce localized inflammation, vasoconstriction, and disruptions in fibrinolysis. Consequently, these changes may lead to focal occlusion of the choriocapillaris, reduced foveal choroidal blood flow, and secondary defects in the RPE, ultimately causing serious macular detachment [175-177].

8.2 Role of gut microbiota in central serous chorioretinopathy

As microbiota can be intervened by probiotics and antibiotics, investigating the relationship linking the gut microbiota to CSC pathogenesis may strengthen the groundwork for such therapeutic modalities [8]. Although the whole-metagenome shotgun sequencing assay detects no significant variations in microbiota composition between CSC patients and a carefully matched control cohort. However, notable functional changes are identified in pathways related to fatty acid metabolism and energy production. The synthesis of the two unsaturated fatty acids, gondoate and cis-vaccenate, is upregulated in the gut microbiota of patients, whereas the tricarboxylic acid cycle and the biosynthesis of L-isoleucine are downregulated [8, 178]. Despite the necessity for further inquiry, these observations suggest that the functionalities of the gut microbiota may serve as a promising target for novel therapies in CSC. Researchers have conducted a comparative analysis of the retinal transcriptome between GF mice fed a normal diet (ND) and those on an HFD. They utilize the high-throughput RNA-sequencing technology to explore transcriptomic alterations without gut microbiota influence. After correlation of raw data, a total of 53 differentially expressed genes (DEGs) are described, with 19 exhibiting upregulation and 34 demonstrating downregulation in GF-HFD mice. These DEGs are implicated in the retinal inflammation pathways, angiogenesis, as well as RPE functionality [179-181]. Functional enrichment analysis shows that the process is critically involved in regulating blood vessel diameter, the inflammatory processes, as well as the negative regulation of endopeptidase activity. Despite the study identified some transcriptomic alterations using the GF mice, further investigation is necessary to elucidate the precise mechanism through which the gut microbiota affects the retinal transcriptome profile. It is believable that future discoveries would provide stimulus for subsequent inquiries into the contribution of the gut microbiota in the context of CSC [181].

9. Gut microbiota and retinal artery occlusion

The retinal circulation is predominantly vascularized by the central retinal artery (CRA), with certain ocular anatomies also receiving from the cilioretinal artery. The principal arterial supply for both of these vessels originates from the ophthalmic artery [182]. Retinal artery occlusion (RAO) is a blindness-threatening condition and represents a final common pathway for several cardiovascular diseases (CVD), most commonly initiated by systemic atherosclerosis [183]. Originally, the central retinal artery occlusion (CRAO) was found in 1859 in the context of a person suffering from endocarditis. The CRAO arises due to the partial or total occlusion of the

CRA, which consequently results in permanent retinal ischemia, irreversible cellular death and catastrophic visual loss [184]. The occurrence of Branch retinal artery occlusion (BRAO) is attributed to obstruction of a branch of the CRA and can cause sudden segmental visual loss, with the potential for recurrence involving other retinal arterioles [182] (Fig. 8). Emboli originating from the internal carotid artery, the aortic arch, or the heart are the primary etiological factors contributing to RAO, referred to as non-arteritic RAO [185]. Rarely, CRA occurs in the context of inflammatory disorders, such as vasculitis, predominantly in patients suffering from giant cell arteritis, which is commonly denoted as arteritic RAO. Conventional teaching paradigms suggest that the majority of severe occlusions are attributable to internal carotid artery pathology [182, 185]. Nonetheless, contemporary evidence indicates that emboli of cardiac origin, particularly those associated with atrial fibrillation, constitute a predominant etiology for acute RAO [186].

The RAO pathogenesis is largely thromboembolic in nature, frequently originating from carotid plaques, thereby establishing a strong correlation between atherosclerosis and RAO [185]. Diet is considered as a predominant contributor for which is positively correlated with both total and low-density lipoprotein (LDL) cholesterol levels, while exhibiting an inversely proportional relationship with high-density lipoprotein (HDL) cholesterol concentrations [187-188]. Aging is another major non-modifiable risk factor of RAO. Registry data demonstrate a pronounced increase in the incidence of all subtypes with advancing age, with the highest frequency occurring in population over 65. This elevated risk likely stems from age-related vascular changes, endothelial dysfunction, and a higher prevalence of systemic conditions such as hypertension and atherosclerosis in the elderly population [189]. The endothelial dysfunction of atherosclerosis facilitates the adherence of platelets, which can secrete chemoattractant and growth factors, thereby exacerbating the progression of plaques. Significantly, evidence from recent study has demonstrated the presence of bacterial DNA within these atherosclerotic plaques, exhibiting phylotypes typically associated with gut microbiota, such as Actinobacteria. These findings provide evidence implicating bacterial translocation in the development of atherosclerotic disorders as a common pathogenic process [190]. Considering the limitation of the therapeutic ways for RAO, the significance of preventive interventions is underscored. In this context, focusing on the gut microbiota as a preventive measure to forestall the progression of atherosclerotic disease, which is the predominant etiology of RAO, may represent a promising and viable strategy.

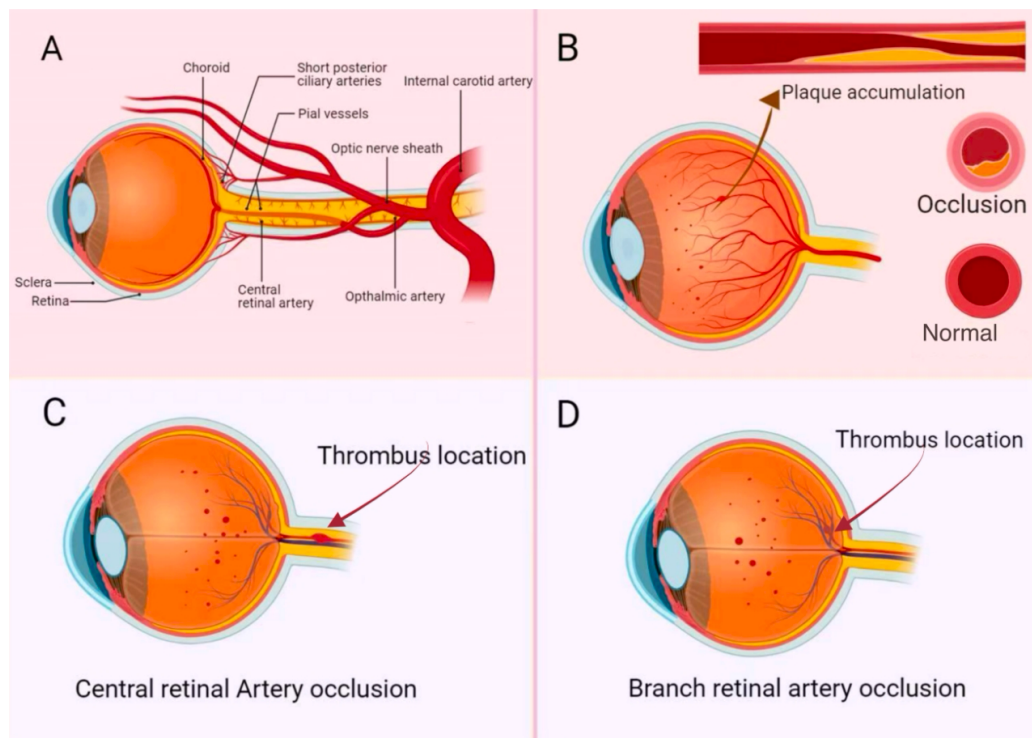


Figure 7. Gut microbiota interventions and CRB1 deficiency in retinal health. (A) Young microbiota transplantation (FMT) reduces retinal inflammation, restores RPE65, and improves gut barrier integrity, while aged FMT exacerbates complement deposition and compromises retinal and intestinal health. (B) CRB1 deficiency disrupts adherens junctions in both the gut and RPE, leading to bacterial translocation, barrier failure, and retinal degeneration. Note. INL, inner nuclear layer; ONL, outer nuclear layer; OLM, outer limiting membrane; LBP, lipopolysaccharide-binding protein; I-FABP, intestinal fatty acid-binding protein.

9.1 Retinal artery occlusion is linked to gut dysbiosis

Researchers have performed sequencing on fecal metagenomes from 29 non-arteritic RAO patients and 30 matched controls to explore links between gut microbiota and the onset of RAO [183]. At the phylum level, the analysis reveals a diminished proportion of Bacteroidetes in comparison with Proteobacteria in the RAO patient samples. Moreover, at a more detailed taxonomic scale, the class Actinobacteria and specific species such as *Bifidobacterium adolescentis*, *Bifidobacterium bifidum*, *Bacteroides stercoris*, and *Faecalibacterium prausnitzii* exhibit increased abundance in RAO patients. Conversely, the family Lachnospiraceae, along with the genera *Odoribacter* and *Parasutterella*, are found to be more prevalent in the control group [183]. Apart from these taxonomic disparities, there is a functional shift in the gut microbiota, particularly with respect to the genes of the methylerythritol phosphate pathway and isoprene biosynthesis, both of which are associated with cholesterol metabolism. Conversely, the microbiota of the control group exhibits an enrichment of metabolites associated with the L-histidine biosynthesis pathway [183]. In particular, a recent study shows that the gut

microbiota metabolic pathways are correlated with the simvastatin targeted treatment, which can diminish the plasma levels of LDL cholesterol [191]. Therefore, modulating the gut microbiota may regulating cholesterol homeostasis and signify a novel therapeutic approach for atherosclerosis and associated ocular vascular disorders.

9.2 Altered Trimethylamine N-oxide levels in retinal artery occlusion

TMAO, a gut microbiota-derived metabolite, serves as a clinical indicator of CVD and has been shown to drive atherosclerosis in preclinical studies [192]. Diverse bacterial strains exhibit varying capabilities in the production of TMAO. In fact, research has established Firmicutes and Proteobacteria as the primary bacterial sources of TMAO. Consequently, the levels of TMAO may be different due to the unique constitution of the gut microbiota [193]. A focused analysis of a subcohort of 12 RAO patients and 11 matched controls have revealed a significantly elevated TMAO concentration in the patient group. MaAsLin-based multivariate approaches have elucidated a negative association between the abundance of *Parasutterella* and *Lachnospiraceae* and TMAO

concentrations, as well as a positive association with Akkermansia abundance. Nonetheless, there is no statistically meaningful variations in TMAO concentrations across the three distinct enterotypes [183]. Moreover, a diminished size of atherosclerotic lesions is noted in a mice knocked-down expression of flavin monooxygenase 3 (an enzyme integral to TMAO synthesis) [194]. The precise role of TMAO in the pathogenesis of atherosclerosis remains to be thoroughly elucidated. It is postulated that TMAO may act as pro-atherogenic molecule, and its association with cardiovascular risk is attributed to its capacity to facilitate foam cell formation and disrupt cholesterol transport [193, 195]. Nevertheless, it remains to be determined whether elevated TMAO levels are causative in RAO development or function merely as an indicator of underlying gut dysbiosis.

10. Microbiota-targeted therapies: opportunities and challenges

We systematically evaluate the evidence for a diverse range of approaches, including probiotics, postbiotics, microbial metabolites, dietary interventions, and other microbiota-modulating strategies, which collectively aim to preserve retina through gut microbiota modulation. The section concludes by delineating the principal opportunities and challenges that will shape the future clinical application of these innovative strategies.

10.1 Probiotic therapies

Probiotic-based biotherapy, which aims to restore gut homeostasis by modulating microbial composition, may effectively slow the progression of age-related retinopathies [125]. Particularly, modulating the systemic immune response via the gut microbiota has surfaced as a promising therapeutic strategy for DR. DR is characterized by a distinct phenotype of gut dysbiosis, notably a depletion of beneficial bacteria such as *Lactobacillus* and *Bacterium*, which has motivated the exploration of probiotic interventions [102]. The promise of this therapeutic approach is further evidenced by studies, in which specific strains, particularly *Lactobacillus paracasei*, can mitigate retinal neurodegeneration and inflammation in DR animal models [196]. In particular, a causal link has been advanced through microbial engineering: an engineered *L. paracasei* strain expressing human ACE2 has been demonstrated to markedly alleviate key DR pathologies, including the formation of acellular capillaries, the loss of RGCs, and the accumulation of inflammatory cytokines [197]. Collectively, these findings suggest that integrating probiotic supplementation and microbial engineering may

act as a compelling therapeutic avenue for DR [102]. This therapeutic paradigm finds strong parallel support in glaucoma research. A pioneering study has demonstrated that a fermented maize product and its liquid fraction, both abundant in lactic acid bacteria, can modulate the gut microbiota in a glaucomatous rat model. These microbial shifts are associated with a downregulation of retinal glial activation, enhanced levels of brain-derived neurotrophic factor (BDNF), and a significant reduction in IOP [125]. While the precise molecular mechanisms bridging these gut changes to retinal benefits necessitates further elucidation, this gut-retina axis crosstalk confers substantial protection to RGCs. This highlights the therapeutic potentials of probiotic interventions in glaucoma management [125].

10.2 Postbiotic therapies

Postbiotic therapy presents a promising strategy by modulating the gut-retina axis for retinopathies. As defined by an “International Scientific Consensus Panel,” postbiotics are “preparations of inanimate microorganisms and/or their components that confer a health benefit on the host” [198]. This definition consolidates various earlier terms, such as “killed probiotics” or “paraprobiotics,” into a unified concept [198]. A key advantage of postbiotics over their live probiotic counterparts lies in their improved stability and safety profile, while still retaining significant biological activity [198]. Evidence for their therapeutic potential is emerging, with studies in aged mice demonstrating that heat-killed *Lactobacillus paracasei* KW3110 modulates the gut microbiota by enriching beneficial bacterial families such as *Bifidobacteriaceae* strains. It also curbs intraocular inflammation by curtailing the population of macrophages responsible for cytokine secretion, thereby preventing age-related photoreceptor loss [69]. Although more clinical research is required, these results highlight the possibility to use heat-killed *Lactobacillus paracasei* KW3110 to treat age-related retinopathies like AMD. Beyond inanimate whole microorganisms, the structural constituents of postbiotics, particularly exopolysaccharides (EPS), represent a promising frontier for DR therapy [103]. EPS are not merely structural components but function as key MAMPs detectable by the host’s immune defenses [199]. A growing body of evidence suggests that the therapeutic potential of EPS in DR is mediated through two principal and interconnected mechanisms: immunomodulation and vascular protection [103]. On one hand, EPS from *Bacillus fragilis* have been shown to ameliorate neuroinflammation by engaging PPRs like TLR2, thereby promoting the enrichment of Tregs. This immunomodulatory shift redirects the host immune response toward an anti-inflammatory state,

marked by a significant increase in the anti-inflammatory factors IL-10 and a concurrent suppression of the pro-inflammatory factors IL-17 [199]. On the other hand, EPS from bacteria like *Bacillus subtilis* confer direct benefits to the retinal vasculature. Experimental studies using the streptozotocin (STZ)-induced diabetic rat models have demonstrated that this vascular protection is achieved by significantly downregulating endothelial adhesion molecules, including ICAM-1 and vascular cell adhesion molecule (VCAM). This reduction is critical for inhibiting leukocyte stasis and infiltration, thus preserving BRB integrity and mitigating microvascular damages [200]. Taken together, the capacity of EPS to cooperatively modulate detrimental immune responses and protect the vascular endothelium underscores their multifaceted potentials as therapeutic agents [103]. Future research should focus on elucidating the precise structure-activity relationships of these EPS and validating their efficacy in trials.

10.3 Metabolite-based therapies

10.3.1 Microbial metabolites of bile acids

Substantial research has identified BAs metabolites as key mediators in retinal health. Both experimental and clinical studies have shown that UDCA and TUDCA, microbial metabolites of BAs, are able to ameliorate retinopathies like AMD and DR [70, 201]. The protective effects of these BAs have been investigated using diverse experimental models. Specifically, TUDCA protects RPE tight junctions and suppresses CNV in an in vitro AMD model. It can also inhibit photoreceptor apoptosis and preserve visual function in murine models of retinal degeneration [202-203]. Systemic administration of UDCA and TUDCA provides neuroprotection for photoreceptors after retinal detachment [70]. The levels of these protective BAs can be enhanced through dietary interventions like chronic IF. Although IF is recognized for its benefits against metabolic disorders and cancer, its role in diabetic microvascular complications is less defined [204]. Some investigations utilizing the db/db mouse model have elucidated the effects of the chronic IF regimen on DR. They find that IF curtails the emergence of acellular capillaries and the infiltration of inflammatory cells in the retina of diabetic mice. Long-term IF is associated with elevated levels of Firmicutes and reduced abundance of Bacteroidetes as well as Verrucomicrobia. This microbial shift, in accordance with the well-established role of Firmicutes in promoting BAs metabolism, results in a significant elevation of TUDCA level [104]. G protein-coupled bile acid receptor 1 (TGR-5), alternatively termed the TUDCA receptor, is present in the RGCs. The TGR5 agonist INT-767 confers

protection against DR in a diabetic mouse model [104]. Collectively, BAs metabolites are established as central players in retinal protection, exerting direct therapeutic benefits against various retinopathies.

10.3.2 Short-chain fatty acids

SCFAs, particularly butyrate, are key microbial products derived from bacterial metabolism that maintain intestinal barrier integrity and immune homeostasis [205]. Investigations in a db/db murine model of T2DM have demonstrated that sodium butyrate supplementation alleviates diabetic endotoxemia through multiple mechanisms, including enhancing gut barrier function via upregulating the levels of tight junction proteins such as zonula occludens-1 (ZO-1) and Occludin. This process reduces inflammatory cytokines and oxidative stress [205]. Interestingly, butyrate can modulate gut microbiota composition by lowering the Firmicutes-to-Bacteroidetes ratio, thereby providing additional protection against T2DM progression [205]. A study investigating DR in a STZ-induced diabetic mouse model has found that butyrate supplementation alleviates the deficiency of plasma butyric acid, 4-methylvaleric acid, and caproic acid [105]. Caproic acid functions as an inhibitor of IL-32 and exhibits anti-inflammatory properties. 4-methylvaleric acid is recognized as a precursor to pogostone. Several lines of evidence have shown that pogostone can mitigate cellular damage induced by TNF- α and LPS through modulating the NF- κ B and nuclear factor erythroid 2-related factor 2 (Nrf2) signaling cascades. This anti-inflammatory and immunoregulatory mechanisms are also linked to gut microbiota remodeling [206]. Accordingly, researchers propose that butyrate may help protect the retina from inflammatory injury by regulating gut microbiota composition and increasing the integrity of intestinal barrier [105]. Additional investigations are required to elucidate the role of sodium butyrate in delaying DR, thus offering new insights for its potential clinical application [105]. In summary, butyrate emerges as a pivotal therapeutic agent linking gut health to retinal integrity. Targeting the gut-retina axis through SCFAs or their microbial producers therefore presents a promising and innovative therapeutic strategy for diverse retinopathies.

10.3.3 Urolithins A

UAs, the metabolites derived from gut microbiota metabolism of dietary complex polyphenols, exert protective effects on retinal neurodegeneration and visual function [73]. For instance, intraperitoneal injection of UAs dampens the retinal damages and maintains the synaptic connectivity in a sodium iodate (SI)-induced

AMD model. Mechanistically, UAs alleviate SI-induced lysosomal membrane permeabilization (LMP) through promoting p62-dependent lysophagy, a process crucial for clearing damaged lysosomes, thereby restoring autophagy flux and mitigating proteostasis defects. UAs attenuate oxidative damage, which is indicated by reduced accumulation of 4-HNE, a marker of lipid peroxidation [207]. Except for AMD, the anti-inflammatory and antioxidant properties of UAs are equally relevant in the context of DR. For instance, UAs administration not only mitigates hyperglycemia, but also ameliorates retinal damage in the STZ-induced diabetic mice, as evidenced by reduced thinning of the ganglion cell layer and improved electroretinogram response [106]. In vitro, HG-induced human retinal endothelial cells (HRECs) are utilized to elucidate the mechanisms underlying the UAs mediated effects. HG conditions promote VEGF secretion and induce BRB dysfunction, while UAs treatment reverses these effects through Nrf2/Heme Oxygenase 1 (HO-1) pathway [208]. The activation of Nrf2/HO-1 pathway also ameliorates the inflammation and oxidative stress in HG preconditioned HRECs. In particular, researchers show that UAs can prevent the histamine-induced vascular damage in a novel ex vivo rat eye model. UAs effectively preserve retinal vascular integrity and inhibit RECs apoptosis, offering a promising alternative to dexamethasone, which is commonly used but associated with severe side effects. Additionally, UAs can modulate microglial activity and inhibit the production of pro-inflammatory factors in an ex vivo rat eye model [209]. Collectively, these findings underscore the therapeutic potential of UAs for both AMD and DR. Although further comprehensive investigations are necessary, this pioneering approach holds great translational prospect for a spectrum of thorny retinopathies.

10.4 Other microbiota-modulating approaches

10.4.1 Dietary interventions

Emerging evidence from a severe acute pancreatitis (SAP) rat model shows that zinc supplementation regulates gut microbiota by enhancing beneficial microbiota (*Bifidobacterium* and *Lactobacillus*) and reducing pathogenic *Escherichia*. This modulation coincides with the downregulation of inflammatory factors (TNF- α and IL-1 β), reduced endotoxemia, and enhanced intestinal barrier integrity [71]. These multifaceted effects underscore zinc's pivotal role in modulating the systemic inflammation and oxidative stress in various inflammatory disorders like AMD [44, 71]. Furthermore, higher dietary intake of omega-3 LCPUFAs correlates with a lower risk for AMD development. Conversely,

elevated omega-6 consumption exerts opposite effects. This evidence indicates that the balance between omega-3 and omega-6 is pivotal in counteracting the sustained subclinical inflammation associated with AMD [72]. In addition to the effects of isolated nutrients, broader dietary patterns demonstrate significant impacts. Greater compliance with the MIND diet correlates with lower OAG risk without influencing IOP [126]. A large-scale population-based study has confirmed this relationship through multivariable conditional logistic regression, showing that a 10% increase in MIND diet adherence correlates with a 20% decrease in OAG incidence [126]. Importantly, this protective effect is independent of IOP, suggesting that the diet's benefits may arise from its capacity to modulate gut microbiota, thereby influencing neuroinflammatory pathways correlated with ocular health.

Having established the role of single nutrients and dietary patterns in retina protection through gut microbiota modulation, recent preclinical studies have progressed to evaluate the synergistic potential of combined nutrient therapies [158]. Investigations using RP models have demonstrated that such combinations confer benefits exceeding direct retinal protection, including the efficacy to modulation of gut microbiota and systemic inflammation [158]. For instance, researchers have successfully established an N-methyl-N-nitrosourea (MNU)-induced murine model of RP to comprehensively evaluate the therapeutic efficacy of two distinct combination therapies: chitosan co-administered with β -carotene, and lutein combined with EGCG [158, 210]. The experimental outcomes reveal that these combinatorial interventions significantly ameliorate RP manifestations. They effectively restore retinal architecture, normalizing both overall retinal thickness and outer nuclear layer dimensions. Of particular significance, these interventions induce substantial alterations in gut microbiota composition, increasing the abundance of beneficial bacterial taxa, including Ruminococcaceae, Lachnospiraceae, and Helicobacteraceae, while enhancing SCFAs production [158, 210]. These findings establish that the therapeutic benefit of such nutrient combinations stems not only from their direct retinal effects but also crucially from their capacity to modulate the gut-retina axis. In summary, the retinal protection conferred by isolated nutrients, dietary patterns, and their combinations stems from a shared set of mechanisms. These include the capacity to modulate gut microbial ecology, enhance intestinal barrier function, and thereby mitigate systemic inflammation and oxidative stress. These multifaceted findings highlight the therapeutic potentials of dietary intervention, heralding the advent of nutritional strategies to treat a range of retinopathies.

10.4.2 Fecal microbiota transplantation

FMT is a procedure that involves transferring prepared fecal matter from a healthy donor to a recipient, aiming to restore the normal gut microbiota profile and its associated functions [36]. This approach is highly effective, with a 90% success rate in treating recurrent *Clostridium difficile* infections after a single treatment [211]. Apart from gastrointestinal disorders, FMT has been used to manage ocular diseases like glaucoma. FMT derived from glaucomatous donors significantly exacerbates retinal inflammation and RGCs degeneration in murine models. Conversely, FMT from healthy donors ameliorates these pathological manifestations through three synergistic mechanisms: restructuring gut microbial ecology to facilitate the colonization of SCFAs-producing bacteria (Lachnospiraceae) while inhibiting pro-inflammatory taxa; modulating metabolic profiles to reduce pro-inflammatory mediators such as LPS and enhance SCFAs biosynthesis, thereby directly mitigating RGC inflammatory damage; and reinforcing intestinal barrier integrity to prevent the translocation of harmful metabolites into systemic circulation [36]. In current clinical practice, FMT is administered via oral capsules, nasogastric intubation, or enema. These modalities have demonstrated favorable safety profiles. However, the ongoing optimization of therapeutic protocols remains an active area of investigation [212]. The continued optimization of its protocols is pivotal in translating these compelling preclinical results into a safe and effective clinical reality, potentially establishing FMT as a groundbreaking option in the therapeutic arsenal for retinal pathologies.

10.4.3 Antibiotics

Antibiotic therapy is conventionally used to treat specific infectious diseases by eliminating bacterial pathogens. However, it is emerging as a potential systemic intervention for ocular diseases such as glaucoma, particularly when linked to chronic gastric infections like *Hp* [35]. For instance, a clinical study involving 41 chronic open-angle glaucoma (COAG) patients and 30 age-matched controls revealed a significantly higher *Hp* infection rate in the glaucoma group. After administration of a triple therapy (omeprazole, clarithromycin, and amoxicillin), patients who achieve eradication of *Hp* exhibit significant improvements in IOP and visual field metrics over a two-year observation period. In contrast, those who remain infected or do not receive treatment show no comparable benefits. These results suggest that chronic *Hp* infection contributes to glaucoma progression, while antibiotic treatment targeting this bacterium could enhance conventional management of the disease [35].

This paradigm establishes *Hp* infection as a potential remote driver of glaucomatous neurodegeneration, thereby opening a new frontier for investigating disease mechanisms and developing complementary treatment approaches.

10.5 Opportunities and challenges

Therapeutic targeting of the gut-retina axis represents a revolutionary opportunity in the prevention and management of age-related retinopathies [46]. This approach capitalizes on the gut microbiota as a master regulator to simultaneously modulate interconnected neural, immune, and metabolic pathways. By addressing these upstream drivers, this strategy can fundamentally alter disease progression, thus offering a paradigm shift beyond the limitations of conventional localized therapies [46]. However, the translation of these promising strategies into clinical practice faces major obstacles. A key obstacle lies in the pronounced host-specific differences in gut microbial makeup, a phenomenon exacerbated by the aging process [213]. This difference complicates the development of universal treatments and inevitably leads to differential patient responses [214]. Current reliance on correlative data from animal models and small-scale human studies makes it difficult to establish causal efficacy and optimize dosing regimens in aging populations [215]. These immediate challenges regarding causality, personalization, and clinical translation represent critical gaps that will be further elaborated in the following section.

11. Challenges and future perspectives: Addressing critical unmet needs

A formidable translational gap exists between bench discoveries and bedside applications in microbiota-based therapies for age-related retinopathies. To bridge this gap, future research must strategically address three fundamental unmet needs.

11.1 Unmet need I: Establishing causal links through longitudinal studies in aging populations

Most current studies are limited to cross-sectional designs that demonstrate correlations between alterations in gut microbiota composition and retinal pathologies, but they cannot establish definite causality or directionality [215]. This ambiguity significantly impedes the advancement of intervention strategies targeting the gut microbiota [8]. Future research should prioritize longitudinal clinical investigations. These studies must systematically monitor microbiota composition, metabolomic profiles, and retinal pathology progression, with a particular emphasis

on aging populations that bear the highest health burden [8]. The comprehensive longitudinal human data is crucial for elucidating whether gut dysbiosis acts as a causative factor or a secondary consequence in retinal pathology. When integrated with findings from randomized clinical trials (RCTs), MR studies, and experimental animal models, they will significantly advance our understanding the gut-retina axis dynamics throughout the human lifespan [8, 215].

11.2 Unmet need II: Pioneering personalized microbiome therapeutics for inter-individual microbiota variability

The composition of gut microbiota is influenced by a multitude of determinants, including genetic factors, dietary patterns, and antibiotic exposure, leading to substantial variations among individuals [214]. This inherent heterogeneity potentially leads to inconsistent or even contradictory outcomes across different patients, which poses challenges for standardized microbiota interventions [214]. To this end, a paradigm shift towards personalized microbiome therapeutics is imperative. This innovative approach integrates multi-omics technologies (metagenomics, metabolomics, and host genomics) to construct comprehensive “microbiome fingerprints” for individual patient [216]. These unique profiles will facilitate customized interventions, thus transitioning from generic probiotics to a new era of precision modulation [216]. The therapeutic protocol encompasses multiple phases: initial functional stratification to identify specific microbial deficiencies, followed by the administration of tailored probiotic and precision postbiotics to address these deficiencies, all complemented by dynamically adjusted dietary regimens to maintain a beneficial gut ecosystem [216]. This personalized microbiome therapeutic is crucial for enhancing the predictability, efficacy, and consistency of microbiota-targeted therapies for retinopathies.

11.3 Unmet need III: Integrating multi-omics to decipher functional pathways for clinical translation

The translation of microbiota-targeted interventions into clinical practice for aging populations is extremely challenging. Heightened inter-individual microbiome heterogeneity will complicate the assessment of therapeutic efficacy and safety [213]. Existing clinical investigations remain constrained by limited sample size, which may significantly impact intervention efficacy and hinder the standardization of outcome [214]. Consequently, future research should prioritize large-scale clinical trials that incorporate integrated metagenomic and metabolomic profilings [213]. This

methodology is critical to transcend chronological age for stratifying the heterogeneous aging population into biologically relevant subgroups, which can be achieved by defining functional microbiome-metabolite fingerprints [213]. These integrations will facilitate the translation of microbiota-based therapies from bench to bedside, ultimately advancing their clinical implementation.

11.4 Cross-cutting technological frontiers

The resolution of the aforementioned core challenges will be significantly accelerated by synergistic advancements in cross-cutting technologies.

11.4.1 Advanced Delivery Systems

Current delivery methods, particularly oral probiotic capsules, are susceptible to inactivation when exposed to gastric acid and bile acids. This leads to suboptimal gut colonization rates and diminished therapeutic efficacy. The development of innovative delivery systems, including power of hydrogen (pH)-responsive microcapsules, nanocarriers, and genetically engineered bacterial encapsulation technologies, has shown promising potential in enhancing the survival rate and targeted delivery of probiotics and their metabolites [217]. For instance, the pH-responsive microcapsule can maintain structural integrity in the acidic gastric environment and release active components when exposed to the neutral pH of the intestinal environment. Nanocarriers exhibit enhanced mucosal adhesion ability and prolonged intestinal retention time through strategic surface modifications. Notably, genetically engineered bacterial encapsulation technology uses modified probiotic strains as carriers to precisely deliver metabolites to specific intestinal regions, thereby optimizing the outcomes of microbiota modulation [217]. These novel approaches would provide promising strategies to address limitations of conventional delivery systems.

11.4.2 Novel Monitoring Platforms

Current methods for real-time, non-invasive monitoring of gut microbiota dynamics and therapeutic responses are inadequate. This significantly restricts the optimization of intervention strategies and refinement of treatment regimens, thus impeding the improvement of therapeutic outcomes for retinopathies and the advancement of precision medicine. Future investigations delineate two promising avenues. Primarily, integrating wearable sensor technology with artificial intelligence (AI) algorithms may hold great potential for real-time gut

microbiota monitoring. Researchers have developed AI-powered wearable systems that leverage the interaction between coil magnetic fields and sensors embedded in pills. These systems achieve AI-driven millimeter-level precision in localizing intestinal pills [218]. This establishes a robust technological foundation for gut monitoring. Secondly, gene editing technologies, especially clustered regularly interspaced short palindromic repeats (CRISPR)-based systems, have shown significant promise in the development of “smart probiotics.” Empirical studies indicate that gene editing enhances the functional adaptability of indigenous probiotics, thus enabling tailored therapeutic applications [219]. Some pioneering studies have engineered *Lactobacillus rhamnosus* GG (LGG) as self-driven

probiotics to carry the CRISPR/Cas9 system. The LGG-mesoporous zeolitic imidazolinium framework-hematoporphyrin monomethyl ether-Cas9/sgrNA complex (LGG-MHS) releases CRISPR/Cas9 through pH-triggered mechanisms in the hypoxic microenvironment. Meanwhile, ultrasound irradiation induces the generation of ROS, which not only accelerates immunogenic cell death (ICD), but also knocks down the IDO1 gene, thereby reversing the immunosuppressive state of the microenvironment. This study demonstrates that CRISPR technology enables probiotics to adaptively regulate their functions in response to environmental signals (such as ultrasound and pH), providing theoretical basis for future application of “smart probiotics” in retinopathies [220].

Table 1. Summary of gut microbiota-related research in age-related retinopathies.

Disease Name	Risk Factors	Classification Of Diseases	Research Models	Test Indicators	Changes in Gut Microbiota	Ref.
AMD	Advanced age, genetics (CFH, ARMS2/HTRA1), HG diet, HFD, etc.	Early-stage (drusen deposits); late-stage (dry AMD, wet AMD)	Mice (HG diet, HFD, laser-induced CNV); human cohorts, etc.	Simpson index, serum cytokines (IL-6, TNF- α), oxidative stress markers (CEP, 4-HNE), macular thickness, etc.	Increased Firmicutes/Bacteroidetes ratio; reduced Bacteroides eggerthii; enriched Prevotella, Holdemanella, Desulfovibrio, etc.	[4, 12, 29, 35, 37-41, 45, 54]
DR	Diabetes mellitus, aging, poor glucose control, insulin resistance, gut dysbiosis, etc.	NPDR; PDR	db/db mice, STZ-induced diabetic mice; human T2DM/DR patients, etc.	Retinal neovascularization, macular edema, LPS, SCFAs, TMAO, VEGF, etc.	Reduced Actinobacteria, Bacteroidetes; increased Shigella; reduced Bifidobacterium, Lactobacillus; decreased butyrate-producing bacteria, etc.	[26, 30, 71, 76-86]
Glaucoma	Elevated IOP, age, Hp infection, genetic factors, etc.	OAG; ACG	Glaucomatous rat models, murine models with FMT; human POAG patients, etc.	IOP, visual field, anti-Hp IgG titer, RGC apoptosis, pro-inflammatory cytokines, etc.	Enriched <i>H. pylori</i> ; altered SCFAs-producing bacteria; FMT from glaucomatous donors exacerbates inflammation, etc.	[112-113, 119-120, 125-127]
Uveitis	HLA-B27, aging, systemic inflammatory diseases, etc.	Anterior, intermediate, posterior; infectious, non-infectious	R161H murine model, HLA-B27 transgenic rats; human AAU patients, etc.	Serum CRP, IL-17, Th17 cell count, ocular inflammation marker, etc.	Enriched Prevotella vulgaris, Akkermansia muciniphila in transgenic rats; elevated Veillonella in human AAU, etc.	[133-134, 141-143]
RP	Genetic mutations, HFD, gut dysbiosis, aging, etc.		rd10 mice, RCS rats, MNU-induced murine, CRB1 mutation models, etc.	Photoreceptor apoptosis, retinal thickness, microglial activation, IL-6, IL-1 α , etc.	Absence of Rikenella spp., Muribaculaceae spp. etc.; enriched Bacteroides caecimuris; altered Proteobacteria, Spirochaetes, etc.	[144, 148, 152-155, 161]
CSC	Psychological stress, aging, corticosteroid use, Hp infection, genetics (CFH, NR3C2), etc.	Acute, chronic, recurrent; simple, complex (by multimodal imaging)	GF mice (HFD), human CSC patients, metabolomic analysis models, etc.	Choroidal thickness, subretinal fluid, fatty acid metabolites (gondoate, cis-vaccenate), etc.	No significant compositional differences but altered functional pathways (fatty acid metabolism, energy production), etc.	[166, 178]

RAO	Atherosclerosis, diabetes, aging, hyperlipidemia, smoking, etc.	CRAO; BRAO	Human non-arteritic RAO patients; murine models with atherosclerotic lesions, etc.	Serum TMAO, cholesterol, bacterial DNA in atherosclerotic plaques, etc.	Reduced Bacteroidetes/Proteobacteria ratio; enriched Actinobacteria, Bifidobacterium adolescentis; reduced Lachnospiraceae, etc.	[187, 194, 195, 199]
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12. Conclusion

This review comprehensively elaborates the bidirectional interaction between the intestinal microbiota and age-related retinopathies. These results highlight the fact that there exists intricate interplay connecting gut microbiota composition to retinopathy (Table 1). Gut dysbiosis may affect the physiological activities of the retina through modulating immune and inflammatory pathways. In particular, products metabolized by the gut microbiota, such as SCFAs and TMAO, contribute to the occurrence and development of retinopathies. These findings provide a robust theoretical foundation for exploring and constructing novel therapeutic strategies for retinopathies. Critically, groundbreaking therapeutic interventions, including FMT and precision probiotics, have demonstrated significant preclinical efficacy in mitigating retinal inflammation and vascular leakage. Although significant progress has been made, tremendous challenges remain unresolved. To address the translational gap, three critical unmet needs warrant prioritization in future research. Firstly, there is an imperative requirement for longitudinal clinical investigations to monitor the microbiota dynamics and disease progression in aged population. Secondly, addressing inter-individual variability necessitates a paradigm shift toward personalized microbiome therapeutics for precise intervention. Thirdly, the integration of large-scale metagenomic and metabolomic profiling is indispensable for future clinical translation. A deeper understanding of how aging affects the gut-retina axis will be essential to developing effective microbiota-based therapies for age-related retinopathies. Encouragingly, the advent of novel technologies and methods presents unprecedented opportunities. By tackling these fundamental challenges and optimizing delivery systems, microbiota-based therapies are anticipated to develop into clinically feasible strategies for the treatment of age-related retinopathies.

Author contributions

Zhihui Feng: Conceptualization; visualization; writing—original draft; writing—review and editing. Kexin Wang: Conceptualization; visualization; writing—original draft; writing—review and editing. Xiaosu Wang: Conceptualization; writing—original draft. Bizhu Zhao:

Writing—review and editing. Zixu Huang: Writing—review and editing. Shenao Ding: Writing—review and editing. Jiehao Zhang: Investigation. Mengli Sun: Visualization. Meiqi Ma: Visualization. Yameng Zhao: Supervision. Yongheng Cui: Supervision. Zongming Song: Funding acquisition; writing—review and editing. Ye Tao: Supervision; writing—review and editing.

Acknowledgements

This work was supported by the Science and Technology Major Project of Henan Province (grant number 221100310200), and the Zhongyuan Science and Technology Leading Talent Project (grant number 2242 00510013).

Declaration of Interest Statement:

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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