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· Review Article ·

# The gut-eye axis in retinal degeneration

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## HIGHLIGHTS

· This review explores the relationship between the gut microbiota and retinal degeneration, focusing on inherited retinal degeneration and age-related macular degeneration.
· Our recent findings demonstrate that bacterial translocation from the gut to the retina contributes to *Crb1*-associated retinal degeneration.
· Future research is warranted to explore the potential parallels between the gut-brain and gut-eye axis, and to investigate whether therapeutic strategies targeting the gut microbiota could benefit both retinal and neural degenerative diseases.

**Abstract:** Retinal degeneration, a leading cause of irreversible blindness, often results from photoreceptor deterioration due to genetic mutations or damage to retinal pigment epithelial (RPE) cells. Emerging research highlights the gut-eye axis, a connection between gut microbiota and eye diseases. Our recent findings demonstrate that bacterial translocation from the gut to the retina contributes to *Crb1*-associated retinal degeneration. This review explores the relationship between the gut microbiome and retinal degeneration, focusing on inherited retinal degeneration (IRD) and age-related macular degeneration (AMD).

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Full Text

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Retinal degeneration, a leading cause of irreversible blindness, is primarily characterized by the deterioration of photoreceptors and/or retinal pigment epithelial (RPE) cells. While genetic mutations in ocular cells are well-established contributors, emerging research highlights the significant role of the gut microbiome in ocular health. The concept of the gut-eye axis posits a connection between the gut microbiota and the development and progression of various retinal diseases, including inherited retinal degeneration (IRD) and age-related macular degeneration (AMD).[1-2] This review explores the intricate relationship between the gut microbiome and retinal degeneration, shedding light on potential mechanisms and therapeutic implications.

## MICROBIOTA AND THE GUT-EYE AXIS

The Human Microbiome Project identified various microbial species - bacteria, viruses, fungi, and archaea - across five distinct regions of the body: gut, oral cavity, vagina, skin and respiratory.[3-6] Gut microbiota is widely recognized as paramount in maintaining our health, including nutrient metabolism, host immunity regulation and protection against pathogens.[7-8] The traditional view has been that the human microbiota begins to develop at birth when the newborn is exposed to the mother's vaginal and intestinal flora. However recent studies have challenged this view by detecting microbial DNA in the placenta, suggesting the possibility of uterine microbiome.[9] After birth, the gastrointestinal tract undergoes rapid colonization characterized by low diversity. As age increases, the diversity of gut microbes also increases and remains relatively stable in adulthood.[10-11] Adult gut microbiota consists of six primary phyla: *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Fusobacteria*, *Verrucomicrobia*, and *Proteobacteria*.[6] The composition of gut microbiota is subjected to shaping by diet, host immune system, and environmental factors such as smoking, depression, surgery, and geographical location.[10,12-14] Gut dysbiosis has been linked to various human diseases.[3]

The gut-eye axis is an intriguing concept in research that highlights the connection between the gut microbiota and ocular health. This concept is an extension of the broader gut-brain and gut-organ axis, showing the systemic impact of gut microbiota on various body systems. Emerging studies suggest that the imbalanced gut microbiota can impact the development and progression of various ocular diseases, including dry eye disease, uveitis, age-related macular degeneration, glaucoma and diabetic retinopathy.[15-19] There is no exact explanation about the detailed mechanisms of the gut-eye axis. The most popular hypothesis is that the gut microbiota or its metabolic products activate retina-specific autoimmune T cells, which then migrate to the eye and mediate the immune response.[20] Our latest research suggests that gut bacteria can reach the retina through disrupted barrier structures, causing fundus lesions in *Crb1* mutant mice.[21] This is the first evidence showing that bacterial translocation could be a key mechanism in regulating the gut-eye axis. It's a growing field with the potential for new therapeutic strategies that could target the gut to benefit ocular health.

## BLOOD RETINAL BARRIER

The concept of the blood retinal barrier (BRB) was first proposed by Schnaudigel.[22] An intact BRB is crucial for the maintaining of the normal structure and stable function of the retina. The BRB functions as a physiological barrier that regulates the movement of ions, proteins, and water into and out of the retina.[23] This regulation is crucial for maintaining the retina's homeostasis and ensuring that the eye remains a relatively privileged site. Structurally, the BRB is composed of two main layers: the inner blood retinal barrier and the outer blood retinal barrier. The inner barrier, comparable to the blood-brain barrier, is formed by the endothelial cells of retinal blood vessels. These cells are tightly joined

by tight junctions, mediating the selective diffusion of molecules from the blood to the retina tissue.[22] The outer BRB is composed of intercellular junction complex between RPE cells, separating the neural retina from the underlying fenestrated choriocapillaris. The RPE delivers blood-derived nutrients to photoreceptors, absorbs light, and carries out phagocytosis of the outer segments of photoreceptors.[23-25]

## STRUCTURE AND FUNCTION OF THE INTESTINAL BARRIER

The human body has multiple mucosal epithelia that form barriers between the external environment and the host internal environment. The gastrointestinal mucosa is a semipermeable barrier with a complex task: permitting the absorption of nutrients, electrolytes, and water while maintaining an effective defense against intraluminal toxins, antigens, and enteric flora.[26] This seemingly contradictory task is achieved through the dynamic interactions between the intestinal mucosa and molecules, maintaining the integrity of intestinal function and immune homeostasis.[27]

The intestinal epithelium is a monolayer of cells that serves as the primary and most significant barrier protecting the body from the external environment. The epithelium preserves its selective barrier function by establishing intricate protein-protein networks that physically connect neighboring cells and seal spaces between them.[28] These protein networks establish three types of adhesive complexes: desmosomes, adherens junctions, and tight junctions.[29] Tight junctions are the uppermost adhesive junctional complex, creating a continuous belt-like structure that encircles the cells. Adherens junctions are located beneath tight junctions, together with desmosomes, providing strong adhesive forces to maintain the integrity of the epithelial structure.

## INHERITED RETINAL DEGENERATION (IRD)

Visual information is a crucial means of survival for humans and animals, with over 80% of external information obtained through vision.[30] Any damage to the structures or functions of the visual pathway could lead to visual impairment. Therefore, the health of the retina, which plays a key role in signaling and processing visual information, largely determines the quality of vision.

IRD is a group of genetic disorders characterized by progressive loss of photoreceptor cells, including Leber's congenital amaurosis (LCA), retinitis pigmentosa (RP), early onset rod-cone dystrophy, cone-rod dystrophy, congenital stationary night blindness, achromatopsia, and Stargardt disease.[31] It is the most common cause of vision loss in the working population in the industrialized countries, with an estimated incidence of 1:2000-3000, affecting 2 million people worldwide.[1,32] More than 300 genes have been linked to IRDs, leading to various manifestations.[33] Broadgate et al. have listed the common mutations and animal models.[31] Clinically, disease diagnosis is typically performed using optical coherence tomography (OCT), autofluorescence imaging (AF), color fundus imaging, combined with electroretinogram (ERG).[31] Due to genetic and clinical heterogeneity, the treatment of IRDs requires highly personalized therapeutic strategies. While neuroprotection, gene therapy, and cell replacement therapy are the proposed approaches for treating different stages of IRDs.[1,34-36] In the past two decades, numerous studies have been carried out to develop safe and effective gene therapy for various inherited diseases and many of these treatments have shown promising results in animal models and have progressed to phase I/IIclinical trials.[36-37] Until now, only one gene therapy correcting the mutations in RPE65 gene (voretigene neparvovec-rzyl) is FDA approved for the treatment of LCA.[37-39] Cell replacement therapy is also a promising strategy for restoring visual function after irreversible retinal cell death in IRDs.[35]

LCA is highly heterogeneous with at least 38 genes involved, and an incidence of 1:30000~80000.[40] Most of those genes are inherited in an autosomal recessive pattern.[41] LCA generally causes early-onset severe visual impairment and its clinical characteristics usually occur within the first year of life, responsible for 20% of childhood blindness.[40,42] Clinically, LCA manifests as early and severe vision loss, nystagmus, nondetectable electroretinogram and abnormal fundus appearance.[40,42]

RP is a genetically heterogeneous condition primarily caused by mutations in over 100 pathogenic

genes, with an incidence of 1:3,000-7,000.[30,32,43-44] Those genes can be transmitted in all models of inheritance: autosomal dominant, autosomal recessive, X-linked, and mitochondrial.[45-47] These mutations lead to progressive death of photoreceptor cells and atrophy of the retinal pigment epithelium cells, which are the hallmarks of RP.[30,43-44] Early-onset RP usually starts around 10 years old and progresses rapidly.[30] RP typically begins with night blindness, which may appear normal or nearly normal during a standard fundus examination. As the condition progresses, there is a gradual concentric loss of the visual field, accompanied by the progressive deterioration of the outer segments of central concave retinal cone cells and significant loss of photoreceptors in the peripheral areas of the retina.[30]

## ROLE OF THE GUT MICROBIOTA IN IRD

The gut microbiota, the community of microorganisms residing in the gastrointestinal tract, plays a crucial role in maintaining overall health and has been increasingly implicated in the pathogenesis and progression of various diseases, including retinal disorders. Nonetheless, there has been limited attention given to the role of gut microbiome in inherited retinal degeneration.

In the Rd10 mouse model of retinitis pigmentosa, notable alterations in the gut microbiome were observed, including microbial dysbiosis marked by variations in alpha and beta diversity across genera, species, and amplicon sequence variant (ASV) levels in comparison to wild type mice. Significantly, four ASVs commonly present in healthy gut microbiome belonging to *Rikenella spp.*, *Muribaculaceae spp.*, *Prevotellaceae UCG-001 spp.*, and *Bacilli spp.*, were absent in the RP mice's guts. In contrast, *Bacteroides caecimuris* was notably enriched in the guts of RP mice.[48]

In our latest study, we investigated the impact of the *Crumbs homolog 1 (CRB1)* gene, which has long been recognized as an important gene whose mutations cause multiple ophthalmic phenotypes, most common forms of LCA and RP.[49] CRB1 is a crucial protein involved in regulating the polarity of cells and intercellular junctions.[50] In Rd8 (retinal degeneration 8) mice bearing a *Crb1* mutation, the gene's expression decreased, and the outer blood retinal barrier and colonic epithelial barrier are compromised, facilitating the movement of the gut microbiota through the body and into the eye, causing macrophage/microglia-mediated (without involvement of T or B cells) fundus damage. However, Rd8 mice raised in a germ-free environment did not show any symptoms of retinal degeneration. Furthermore, we found that systemic antibiotic administration or gene therapy performed locally in the intestine can effectively alleviate retinal damage.[21] Our research suggests that novel therapies controlling systemic bacterial translocation or combining both systemic antimicrobial treatments and local gene therapies are needed in order to cure *Crb1* associated retinal degenerative diseases. This work demonstrates that direct bacterial translocation might be an additional mechanism regulating the gut-eye axis. Consequently, translocated bacteria-dependent intraocular inflammation may also contribute to ocular diseases beyond IRDs, such as uveitis and AMD.

## AGE-RELATED MACULAR DEGENERATION (AMD)

AMD, the leading cause of incurable blindness among individuals older than 55 years, is characterized by central vision impairment, posing a threat to high-acuity central vision necessary for critical activities like reading, driving, and identifying faces.[51] As the global population ages, AMD has become an important public health concern. It is projected that the number of individuals affected by AMD could exceed 280 million by 2040.[52] Early-stage AMD is characterized by clinical signs such as drusen and abnormalities in the retinal pigment epithelium. Advanced AMD is classified into neovascular AMD (also known as wet, or exudative AMD) and geographic atrophy (also known as dry, or non-exudative AMD).[2,51,53-54] Despite advances in detection technology, the exact pathogenesis of AMD remains to be elucidated. Studies have shown that the composition of the gut microbiome can impact systemic inflammation, immune responses, and metabolic processes, all of which are known to be involved in the development and progression of AMD.[55] Genome-wide association studies (GWAS) have identified genetic

variants associated with AMD.[56-58] Genes involved in complement and immune regulation were significantly enriched by pathway analysis of AMD candidate genes.[56,58]

AMD was traditionally diagnosed through clinical examination or by evaluating color fundus photographs. Advances in retinal imaging have uncovered biomarkers indicative of the progression of AMD. OCT provides high-resolution images of the retina, helping in the detection, classification, and monitoring of AMD.[59] Fundus autofluorescence (FAF) utilizes endogenous fluorophores in the eye to image the retina, helping in identifying, quantifying, and tracking areas of RPE loss.[60] OCT angiography (OCTA) non-invasively images the vascular beds of the eye without contrast agents, aiding in the detection of blood flow abnormalities.[61-62] Indocyanine green angiography (ICGA) provides information on the choroidal vasculature and can be used in the assessment of AMD.[63] These imaging techniques have revolutionized the understanding and management of AMD by enabling detailed visualization of retinal structures and changes associated with the disease progression. Multiple imaging techniques offer additional insights and complementary information about AMD.

## POTENTIAL ROLE OF BACTERIA IN AGE-RELATED MACULAR DEGENERATION

The gut microbiota plays an essential role in AMD by influencing the risk and pathogenesis of the disease. Several studies have found AMD is associated with gut dysbiosis, characterized by an imbalance in the intestinal microbial composition compared to that of healthy controls. Research indicates that mice with induced choroidal neovascularization, a model for AMD, exhibit a notable shift in their gut microbiota composition compared to healthy mice, with a higher relative abundance of *Candidatus saccharimonas*.[64] Rowan and colleagues conducted a comparison of gut microbiome composition in mice with and without the AMD phenotype using 16S rDNA sequencing.[65] Their analysis revealed notable variations in the gut microbiome taxa influenced by diet. Furthermore, they identified *Clostridia* and *Bacilli* as potential risk factors for AMD. Mice on a high glycaemic diet have an increased risk of developing AMD, whereas a low glycaemic diet has a protective effect against the disease.[17,65-66] Although the exact mechanisms remain unclear, it is known that hyperglycaemia can lead to dysbiosis by promoting the growth of *Clostridiales* at the expense of *Bacteroidales*.[17] Apart from animal research, Zinkernagel et al. discovered that the bacterial genera *Anaerotruncus*, *Ruminococcus torques*, and *Eubacterium ventriosum* were more prevalent in patients with AMD, whereas *Bacteroides eggerthii* was enriched in controls.[67] The relative abundance of *Ruminococcaceae* and *Prevotella* is increased in AMD patients.[68] Notably, *Ruminococcus* can degrade mucin and *Eubacterium* can stimulate the production of IL-6 and IL-8 cytokines.[69-70] These actions may lead to heightened gut permeability and inflammation, potentially impacting distant organs like the eye.

The gut-eye axis can influence retinal health through various mechanisms. Rowan et al. suggest that many metabolites produced by gut microbiota reach the retina and potentially impact retinal function[17]. Zhang and colleagues utilized a laser-induced mouse model that exhibited characteristics resembling AMD, such as neovascularization and inflammation. By comparing germ-free (GF) mice with specific pathogen-free (SPF) mice on a standard diet, they observed that GF mice showed decreased neovascularization and peripheral microglial infiltration.[71] This observation confirmed that certain AMD-related alterations are influenced by the gut microbiome, suggesting a correlation within the gut-eye axis. Contrary to the traditional belief that the intraocular environment is sterile, additional recent studies have shown evidence of the existence of ocular microbiota. Deng et al. have shown that microbial communities may inhabit the human intraocular cavity, with disease-specific microbial signatures detected in individuals with AMD and glaucoma.[72] Imbalances in this microbiota could potentially trigger or exacerbate inflammatory processes involved in AMD.

In AMD, the outer blood-retinal barrier is compromised. Golestaneh et al. have found that the RPE from AMD donors exhibits notable functional deficiencies, characterized by heightened oxidative stress and diminished autophagic activity in comparison to

normal RPE, making them more susceptible to damage.[73] AMD initially impacts the RPE, and as the disease progresses, leads to secondary loss of photoreceptor cells.[74-75] However, the exact causative factors leading to impairment of the RPE cell layer remain unknown.

## TARGETING BACTERIA FOR THE TREATMENT OF OCULAR INFLAMMATION

Beyond degenerative eye diseases, intraocular disorders such as uveitis and glaucoma have been associated with dysbiosis of the gut microbiota. Therefore, targeting the global and local microbiota may provide a comprehensive strategy for managing these ocular inflammatory conditions.

Multiple strategies can be employed to target the gut microbiota for the treatment of ocular diseases, contingent upon the underlying molecular mechanisms. For instance, when pathogenic bacteria colonize the gut or eye and trigger ocular inflammation, targeted antibiotic therapy may be necessary to eradicate the infection and reduce inflammation. In cases where dysbiosis of the gut microbiota leads to imbalanced microbial metabolites or dysregulated immune responses, interventions such as fecal microbiota transplantation (FMT), probiotics, prebiotics, or synbiotics may be beneficial in restoring a healthy gut microbiome and controlling the ocular manifestations. For genetic disorders like *Crb1*-associated retinitis pigmentosa, a combined approach involving antibiotics to control microbial translocation and strategies to repair the compromised barriers in the gut and eye may be required.

## CONCLUSION AND FUTURE DIRECTIONS

The interaction between gut microbiota and eye diseases is an emerging area of research, shedding new light on the potential mechanisms through which gut microbiota may influence ocular health. This review highlights important studies that connect the gut microbiome with inherited retinal degeneration and age-related retinal degeneration. Those studies support the existence of a gut-eye axis. There is growing evidence that gut bacteria can translocate to the eye, directly affecting the onset and progression of eye diseases.[21] However, whether similar gut-eye axis regulatory mechanisms exist in other eye diseases, particularly immune-related eye conditions such as uveitis, diabetic retinopathy and AMD, remains to be studied. Further research is needed to fully understand these interactions and to explore potential therapeutic strategies targeting the gut microbiota to prevent or slow the progression of retinal diseases.

Similar to the eye, the brain is also considered an immune-privileged site. The bidirectional communication between the gastrointestinal tract and the central nervous system, particularly the brain, forms an intricate network that influences a wide range of physiological and psychological processes. Beyond neurotransmitter production and metabolic and immune system regulation, the brain exerts neural control over gut function and microbiota composition. Future research is warranted to explore the potential parallels between the gut-brain and gut-eye axes, and to investigate whether therapeutic strategies targeting the gut microbiota could benefit both retinal and neural degenerative diseases.[76]

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### Author Contributions

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(III) Provision of study materials or patients: None
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## Conflict of Interests

Lai Wei is a founder and consultant for PrecVision Ltd. All other authors declare no competing interests.

## Patient consent for publication

None

## Ethical Statement

None

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This article was a standard submission to our journal. The article has undergone peer review with our anonymous review system.

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None

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