Advances in Ophthalmology Practice and Research 5 (2025) 165–174

Contents lists available at ScienceDirect

Advances in Ophthalmology Practice and Research

journal homepage: www.journals.elsevier.com/advances-in-ophthalmology-practice-and-research

Review

Gut-eye axis

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ARTICLE INFO

Keywords:
Gut-eye axis
Gut microbiota
Ocular disease
The leaky gut
Microbial-derived metabolites
Immune dysregulation

ABSTRACT

Background: The gut microbiome, colonizing the human gastrointestinal tract, is increasingly recognized for its symbiotic relationship with the immune system in maintaining overall host health. This emerging understanding raises intriguing questions about potential connections between the gut microbiome and anatomically distant organs, such as the eye, possibly mediated through immune pathways.
Main text: This review synthesizes contemporary research on ocular diseases with the framework of the burgeoning "gut-eye axis" concept. Investigations spanning from the ocular surface to the fundus suggest correlations between the gut microbiome and various ocular disorders. By elucidating the putative pathogenic mechanisms underlying these ocular conditions, we offer novel perspectives to inform future diagnostic and therapeutic interventions in ophthalmology.
Conclusions: By presenting a critical analysis of current knowledge regarding the role of gastrointestinal microbiota in ocular health, this review shed light on the complex interplay between gut dysbiosis and eye disorders. Our work endeavors to catalyze interdisciplinary research and foster innovative clinical applications, thereby bridging the gap between the gut microbiota and the ocular well-being.

1. Introduction

"All disease begins in the gut."

–Hippocrates of Kos (Hippokrátēs ho Kṓos: c. 460–c. 370 BCE)

Long before the modern era, approximately 2000 years ago, the Hippocrates, regarded as "the father of the modern science", had made this profound observation.[1,2] Over the decades, scientific inquiry has intensified, focusing on elucidating the intricate relationship between the gastrointestinal system and overall host health.[3–5] The gut microbiota (GM), the predominant component of the gastrointestinal environment, has emerged as a critical factor in maintaining host homeostasis through its complex interactions with the immune system.[6] This burgeoning field of research has led to the establishment of various conceptual frameworks linking GM to diverse medical disciplines, including the gut-brain axis, gut-lung axis, gut-liver axis, and etc.[1,7–10] Given this expanding understanding, it raises the question of whether the GM can exert any influence on the eye – an organ anatomically distant from the gastrointestinal tract—and, if such a relationship exists, what mechanisms underpin this putative connection.

This review article endeavors to summarize contemporary research on ocular diseases, elucidating potential pathogenesis mechanisms while concurrently establishing the fundamental tenets underlying the nascent concept of the gut-eye axis. By introducing this rapidly expanding field of research, we seek to foster a transformative approach to understanding and management of certain eye diseases. Our review aims to illuminate novel perspectives that may precipitate significant advancements in both diagnostic methodologies and therapeutic interventions within the field of ophthalmology.

2. Influence of the gut microbiome

2.1. The role of gut microbiome in human health

The human gut microbiome, often referred to as "the second genome of the human body", comprises a myriad of microorganisms including bacteria, viruses, archaea, and eukaryotes along with their genetic entities inhabiting the gastrointestinal tract. There are several essential functions conferred by the gut microbiome on the human host, such as nutrient metabolism, removal of toxic compounds, defense against

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https://doi.org/10.1016/j.aopr.2025.01.003
Received 17 October 2024; Received in revised form 19 December 2024; Accepted 14 January 2025
Available online 27 January 2025

pathogens, strengthening of the intestinal barrier, and stimulation and modulation of the immune system.

The human gut microbiome, often referred to as "the second genome of the human body", comprises a myriad of microorganisms including bacteria, viruses, archaea, and eukaryotes along with their genetic entities inhabiting the gastrointestinal tract.[11] The gut microbiome, having coevolved with human hosts over at least a billion years of colonization, confers multiple critical functions to their hosts. Three primary roles are particularly noteworthy: (1) defense against pathogenic microorganisms, (2) acquisition of nutrients, and (3) intricate interactions with the host immune system.[12,13]

Commensal microbiota residing in the gut employ multifaceted strategies to prevent colonization by potentially harmful exogenous microorganisms. These defensive mechanisms include the production of bacteriocins—antimicrobial peptides that directly inhibit pathogenic growth, competitive nutrient sequestration that limits resource availability for invading microbes, and strategic modulation of host immune responses to enhance systemic and mucosal defense capabilities.[14]

The metabolic contributions of GM are profound, significantly influencing energy homeostasis and body composition. These microbial ecosystems generate metabolites that contribute an estimated 5%–10% of the host's daily energy requirements.[15] Notably, certain microbial metabolites, such as branched-chain amino acids (BCAAs), imidazole propionate, and bacterial lipopolysaccharides (LPS), have been implicated in metabolic perturbations, particularly insulin resistance.[16]

The immunological dialogue between GM and the host immunity represents a dynamic and multifaceted relationship. These commensal microorganisms orchestrate immune system development from early life, continuously modulating immune responses throughout the host's lifespan.[6,17] They mainly communicate through their metabolites. Short-chain fatty acids (SCFAs), generated through microbial fermentation of dietary fibers, exemplify this intricate communication. This microbial byproduct can induce and develop RORγt $^{+}$ T_{reg} cell subset during early life of mice.[18] It also demonstrates remarkable immunomodulatory capabilities by binding to G protein-coupled receptors (GPCRs), which enhance epithelial barrier integrity and promote immune tolerance. Beyond local interactions, SCFAs exhibit systemic effects, traversing physiological boundaries to influence distant organ systems. Their capacity to modulate antigen-presenting cells extends to neural and respiratory environments, potentially mitigating inflammatory responses associated with neuroinflammation and allergic airway conditions.[6]

2.2. The impact of gut dysbiosis on diseases

Although there is currently no exact definition of the healthy human microbiome on the level of the taxonomic features, it is believed that an elevated taxonomic diversity, substantial microbial gene richness as well as stable microbiome functional cores characterize healthy gut microbial communities.[19] In some cases, the process of aging, the overuse of antibiotics, certain diets, etc. May induce a disruption in the composition or function of this healthy GM, defined as dysbiosis, subsequently disrupting the homeostatic state, interfering with the host immune system and thereby contributing to certain diseases that encompass a wide spectrum including gastrointestinal inflammatory and metabolic disorders as well as neurological, cardiovascular, and respiratory illnesses. Emerging evidence from both human and animal studies has demonstrated a profound correlation between GM dysbiosis and diverse pathological conditions, including inflammatory bowel disease, obesity, diabetes mellitus, autism spectrum disorder, systemic autoimmune conditions, and even cancer have association with the gut dysbiosis.[20–26] The perturbations within the gut microbial community have also been implicated in ocular diseases.

3. Gut microbiota and ocular disease

3.1. Ocular surface disease

3.1.1. Chalazion

Chalazion commonly presents as a gradually enlarging eyelid nodule, sometimes accompanied by eyelid discomfort or temporary astigmatism due to the compression of the nodule. It is considered as a chronic granulomatous reaction induced by retained sebaceous secretions from the meibomian gland.

There are several risk factors including blepharitis, rosacea, prior chalazion, Demodicosis (Demodex mite infestation), low serum vitamin A, gastrointestinal inflammation, and smoking, etc.[27] Recently, some clinical studies supported a link between gut dysbiosis and the chalazion. Cui et al. discovered that despite similar gut diversity in chalazion and healthy children, certain bacterial species (*gut_metagenome*, *human_gut_metagenome*) differ significantly. *Gut_metagenome*, belonging to *the Sutterella genus*, may play a role in the formation of the chalazion among children and is strongly correlated with the number, rupture, and postoperative recurrence of the meibomian cysts in children.[28] In addition, studies showed that probiotic supplementation, composed of a mixture of live cells of *Lactococcus lactis*, *Streptococcus thermophilus,* and *Lactobacillus delbrueckii* subsp, can boost the efficacy of conventional therapies by promoting the full resolution of chalazion faster, easily and feasibly.[29]

3.1.2. Corneal disease

Given the established correlation between GM and numerous diseases, some research has been conducted to investigate a potential connection between GM and corneal disease, along with the underlying mechanisms. Corneal disease, a type of vision-threatening disease, includes various causes such as inflammation, trauma, congenital abnormalities, degeneration, tumors, etc.

Among them, infectious keratitis is the primary cause of corneal blindness.[30] A study suggested that gut bacterial and fungal microbiota perturbations are linked to bacterial keratitis.[31] In addition, evidence has demonstrated that a decreased diversity of the gut bacterial microbiota was observed in individuals suffering from fungal keratitis.[32] To explore the potential mechanism underlying this correlation, Kugadas et al. carried out a study examining the influence of microbiota on susceptibility to Keratitis induced by ocular *Pseudomonas aeruginosa.* They noted that, in a healthy state, microbiota boosted the eye's natural immune defenses by raising the levels of immune substances in tears, including secretory IgA and complement proteins, while removing eye or GM, especially removing the latter, may lower resistance to infectious keratitis. They suggested that GM initiated the development of neutrophils in the bone marrow, thereby regulating the pool of neutrophils and their activation state, and along with the eye microbiota they induced neutrophil recruitment to the ocular tissues during infection in an IL-1β-dependent manner.[33]

In developing countries, particularly those embroiled in wars or civil conflicts, trauma frequently serves as the primary cause of unilateral vision loss. Corneal injury, a common ocular trauma, can also cause blindness if the corneal wound does not heal properly.[34] An observational study has linked GM alterations in diabetic mice to delayed corneal wound healing via a weakened systemic immune response, marked by impaired T-cell proliferation, and subsequent local immune dysfunction characterized by reduced chemokine and growth factor production in the tear film.[35] To further explore the causal relationship between gut dysbiosis and corneal injury, another research revealed that gut dysbiosis, triggered by a high-fat diet, modified genes related to epithelial function and corneal immunity in mice, shifted the distribution of corneal immune cells including Ly6G+ and γδTCR + immune cells, and consequently influenced the corneal response to injury. Notably, fecal transplantation

normalized the delayed epithelial healing observed in high-fat diet-fed mice.[36] While antibiotics are crucial in treating corneal injury, they may impede corneal nerve regeneration by inducing GM dysbiosis, which affects corneal CCR2$^-$ macrophages responsible for neurotrophin expression.[37]

3.1.3. Dry eye disease

Dry eye disease (DED), a widespread ocular surface disease impacting 5%–50% of individuals globally, is a general term that describes the condition of the anterior segment of the ocular structure in reaction to a disruption in the tear film.[38]

A study demonstrated that patients with DED exhibited deviations in the *Firmicutes/Bacteroidetes* ratio, a known indicator of gut health, which implied a link between gut dysbiosis and DED. Compared to healthy individuals, those with DED showed decreased levels of *Faecalibacterium*, *Bifidobacterium*, and *Parabacteroides* genus.[39,40] In addition, an excess of *Lactobacillus* and *Bifidobacterium*, along with a deficiency of specific species notably *Fusobacterium varium* and *Prevotella stercorea*, was observed in patients with Sjögren's-related dry eye.[41].

DED is now understood as an inflammatory cycle that can be triggered or intensified by extrinsic and intrinsic factors. These factors can compromise tear instability and composition, including hyperosmolarity, ultimately culminating in corneal, conjunctival, and lacrimal gland epithelial disease.[42] Dysbiosis is one of these risk factors.[43] The proposition of the "Gut dysbiosis–Ocular surface–Lacrimal gland Axis" hypothesis elucidated gut dysbiosis in instigating DED via five distinct mechanisms.[39,40] These encompassed myeloid cell migration theory, effector lymphocyte imprint theory, molecular mimicry theory, metabolite circulation theory, and neuropeptide circulation theory (Fig. 1.).

According to another study, patients with immune-mediated dry eye reported improved DED symptoms after undergoing the fecal microbial transplant, suggesting its potential as a therapeutic option for individuals with DED.[44]

3.2. Glaucoma

Glaucoma, the predominant reason for permanent vision impairment, is typified by the progressive deterioration of retinal ganglion cells (RGCs) and their corresponding optic nerve axons.[45,46] The diagnosis of glaucoma typically hinges on the presence of optic disc cupping, defects in the visual field, and possible high intraocular pressure (IOP). Nevertheless, emerging evidence suggests that factors beyond and related to IOP significantly contribute to the onset and progression of glaucoma.[47] Recently, the association between microbiota and glaucoma has garnered increasing attention, given the established understanding that the gut dysbiosis can lead to neurodegenerative diseases.[48]

Evidence showed that microbiota may influence the progression of glaucoma by modulating metabolite levels. For instance, increased taurocholic acid and decreased glutathione are associated with reduced retinal ganglion cell survival.[48] Another study suggested that microbial heat shock proteins (HSPs) stimulate T-cells, leading to the production of HSP-specific autoreactive T-cells through a process known as antigenic mimicry. This process then mediates the loss and degeneration of RGC axons.[49,50] (Fig. 2.) Research has shown that elevated levels of SCFAs

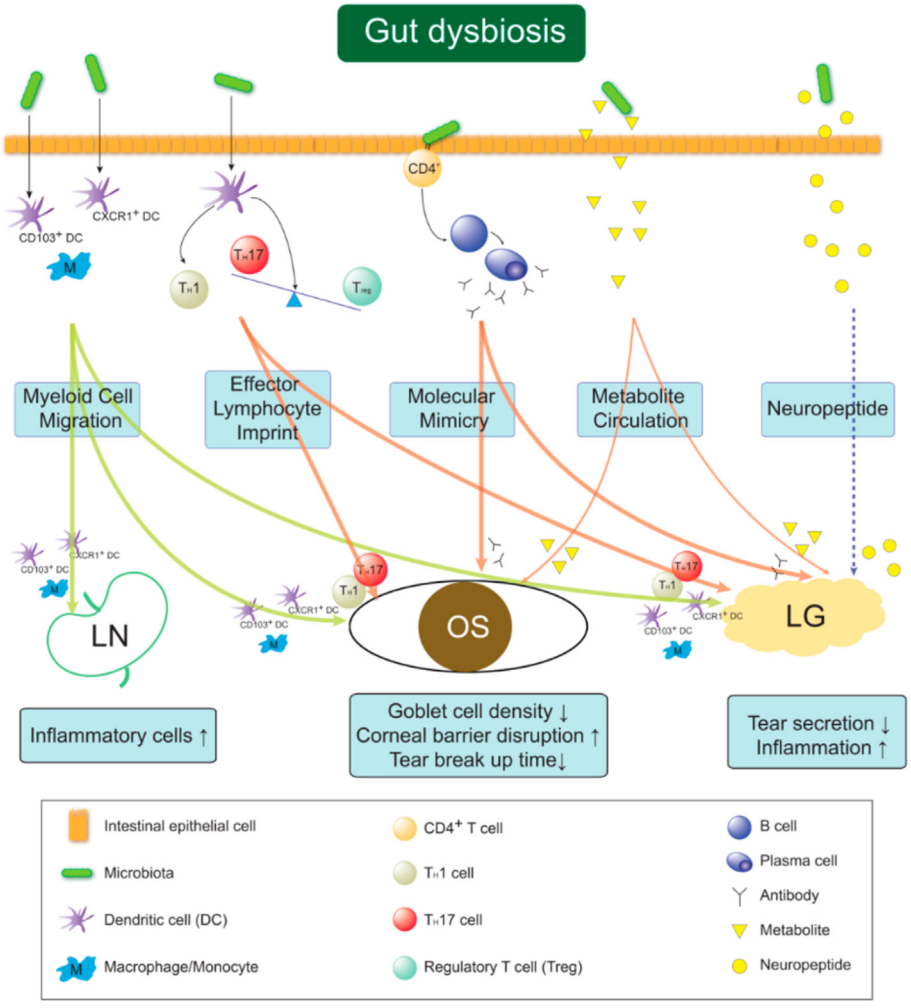

Fig. 1. The hypothesis of Gut dysbiosis–Ocular surface–Lacrimal gland Axis.[39]
Gut dysbiosis may induce dry eye disease by the following five mechanisms. Myeloid cell migration theory: Gut dysbiosis-mediated CD103$^+$ or CXCR1$^+$ dendritic cells or monocyte/macrophages migrate to drainage lymph nodes, ocular surface and lacrimal glands in order to prime T cells or secrete pro-inflammatory cytokines. Effector lymphocyte imprint theory: Gut-derived helper T 1 (Th1) and 17 (Th17) cells migrate to the ocular surface and lacrimal gland, or gut-derived Treg cells are less circulated. Molecular mimicry theory: Microbial-derived antigens cross-prime autoreactive CD4$^+$ T cells helping B cells to produce autoantibodies. Metabolite circulation theory: Microbial metabolites, such as short-chain fatty acids, decrease to enter systemic circulation reaching ocular surface and lacrimal gland. Neuropeptide circulation theory: Homeostatic circulation of gut-derived neuropeptides is distributed to reach lacrimal gland and influence tear secretion.

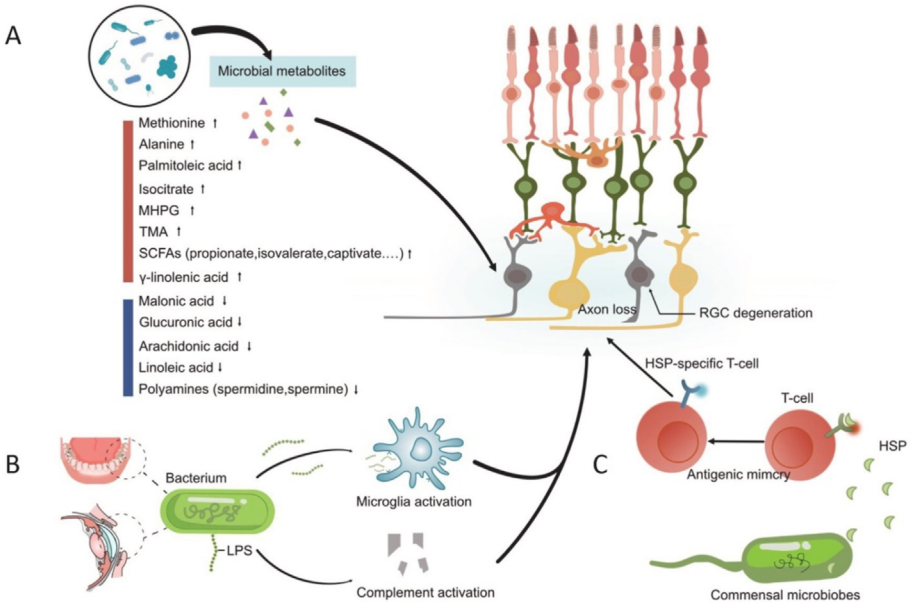

Fig. 2. Microbe-derived metabolites, microbes-activated LPS-TLR4 pathway, and HSP-mediated T-cell activation in glaucoma.[49]
Various microbe-derived metabolites are altered in glaucoma patients, suggesting metabolites may play crucial roles in glaucoma development. Bacterial LPS triggers an upregulation of TLR4 and the complement system in the retina. Microbial HSPs activate T-cells, producing HSP-specific autoreactive T-cells by antigenic mimicry, mediating RGC axon loss and degeneration.HSP, Heat stress protein; LPS, lipopolysaccharide; MHPG, 3-Methoxy-4-hydroxyphenylglycol; TLR4, toll-like receptor 4; TMA, trimethylamine.

were linked to a higher prevalence of primary open-angle glaucoma, mediated by retinal microglial activation and altered expression of retinal microRNAs, such as MiR-122-5p, ultimately causing retinal inflammation and RGC loss.[51] These findings highlight the potential of modulating gut microbiota-derived metabolites as a novel therapeutic approach for glaucoma.

3.3. Ocular fundus disease

3.3.1. Uveitis

"Uveitis", is a term collectively used to categorize intraocular inflammatory conditions that impact the uveal tract and the retina, which can be either infectious or noninfectious in origin, while the latter is often referred to as "immune-mediated uveitis". The prevailing view is that most instances of immune-mediated uveitis stem from an imbalance between regulatory mechanisms and inflammatory mechanisms, potentially triggered by environmental factors and genetic predispositions.[52] In recent decades, there has been escalating attention regarding the impact of the GM on the immune system as well as the immune-mediated diseases, uveitis being one of them.

A study demonstrated a reduction in microbiota-related secondary bile acid concentration in feces and serum of animals with EAU. Furthermore, the severity of EAU lessened upon gut bile acids pool restoration, linked to the inhibition of nuclear factor κB-related pro-inflammatory cytokines in dendritic cells.[53] An animal experiment revealed that fecal microbiota transplantation from patients diagnosed with Behcet's disease notably amplified the synthesis of inflammatory cytokines including IFN-γ and IL-17, and escalated the severity of experimental autoimmune uveitis (EAU).[54]

To elucidate the underlying processes through which GM impact the onset of immune-mediated uveitis, four primary interrelated mechanisms have been proposed.[55] (Fig. 3.)

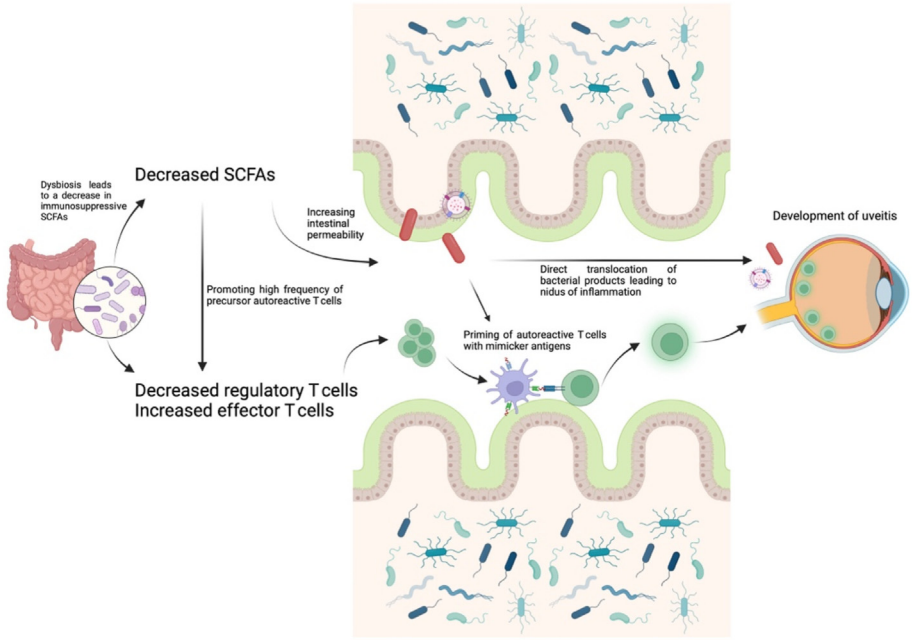

Fig. 3. Four interrelated proposed mechanisms of the intestinal microbiome that lead to ocular autoimmunity, and the gut-eye axis.[55]
Dysbiosis leads to a decrease in SCFAs, among other intestinal changes. These alterations promote increased intestinal permeability and an imbalance of T cells with an excess of effector T cells and a loss of regulatory T cells. Excess effector T cells are activated by mimicker microbial antigens primed against host ocular antigens (molecular mimicry) and cause uveitis. Increased intestinal permeability leads to translocation of bacterial products to remote host locations (including the eye), causing a nidus of inflammation. SCFAs, short-chain fatty acids.

There are also several potential treatment strategies for autoimmune uveitis by targeting the GM, including the use of antibiotics to rectify the dysbiosis linked with uveitis, the application of bacterial metabolite SCFAs to inhibit the movement of effector T cells from the gut and encourage regulatory T cells, and modifications in diet to boost SCFA production, which in turn reduces intestinal permeability.[56] (Fig. 4.) Nakamura et al. established that oral antibiotics regulated the severity of EAU by altering T lymphocyte subsets in the gut and beyond.[57] Similarly, they discovered that oral short-chain fatty acids (SCFA) administration could mimic these effects by modifying T-cell subsets, enhancing gastrointestinal homeostasis, and restricting the migration of effector T cells from the gut to other tissues.[58]

3.3.2. Retinopathy

3.3.2.1. Diabetic retinopathy. As a frequent complication of diabetes mellitus (DM), diabetic retinopathy (DR) ranks among the leading causes of preventable vision loss in the economically active population, representing a substantial public health challenge. As the prevalence of DM continues to rise, so does the incidence of DR, underscoring the critical need for ophthalmic healthcare systems to strengthen their capacity in anticipation of increased demand for specialized care and treatment.[59] Despite considerable progress in the treatment of DR, particularly with therapy targeting vascular endothelial growth factor (VEGF), current interventions are largely confined to managing the advanced stages of the disease and require recurring intravitreal injections. Additionally, anti-VEGF therapy and surgical procedures are not always effective in preventing further visual deterioration. As a result, there is an urgent need to explore novel therapeutic strategies for early-stage intervention in DR.

The burgeoning field of GM research, now broadly acknowledged as a significant contributor in metabolic disorders, prompts an assumption that there might be an association between dysbiosis and DR. Comparative analyses have revealed distinct GM compositions between individuals with DR and healthy controls, as well as between diabetic patients with and without DR.[60] Additionally, analysis of the GM in patients with DR through 16S rRNA sequencing has identified *Bacteroidetes*, *Firmicutes*, *Proteobacteria*, and *Actinobacteria* as the predominant phyla.[61] A diminution in the genus *Pasteurellaceae* was noted as a potential predictive biomarker for DR in another study.[62]

Several mechanisms have been proposed to elucidate the connection between GM and DR.[63,64] Increased gut permeability and subsequent dysbiosis-induced microbial translocation facilitate the absorption of some microbiota-derived metabolites, including branched-chain amino acids (BCAA), lipopolysaccharides (LPS), and trimethylamine-N-oxide (TMAO). These metabolites contribute to insulin resistance, dyslipidemia, and increased pro-inflammatory cytokine secretion, ultimately influencing DR pathogenesis. Conversely, other microbiota-derived metabolites, such as SCFA and tauroursodeoxycholic acid (TUDCA), may exert protective effects against DR progression, illustrating the dual nature of GM's influence on this condition (Fig. 5.).

Given that inflammation response and gut barrier dysfunction may accelerate DR progression, researchers have explored strategies to prevent this "leaky gut". A recent investigation revealed that dysregulation of the intestinal renin-angiotensin system can intensify systemic inflammatory processes, contributing to DR pathogenesis. Remarkably, preserving intestinal angiotensin-converting enzyme 2 (ACE2) activity and thus elevating gastrointestinal angiotensin 1-7 levels may restore gut barrier integrity, potentially offering a new strategy to mitigate DR development.[65]

3.3.2.2. Age-related macular degeneration. Predominantly affecting individuals over the age of 55, age-related macular degeneration (AMD) accounts for 6%–9% of legal visual impairment worldwide.[66] The gradual accumulation of oxidative damage as a consequence of the natural aging process leads to intracellular waste buildup, setting off a series of harmful events. These include retinal pigment epithelium (RPE) dysfunction, abnormal extracellular matrix deposits (drusen), complement system activation, and choriocapillaris degeneration. Collectively, these events result in severe hypoxia and persistent inflammation in the eye, further exacerbating oxidative damage to the retina and ultimately culminating in the death of photoreceptor cells.[67]

Besides advanced age, there are also several risk factors relating to AMD, including genetic mutations, smoking, dietary habits, etc. Evidence from numerous studies has demonstrated a significant association between dietary patterns and AMD.[68–70] This lends plausibility to the inference that AMD could be linked to the GM through dietary influences or other mechanisms.

In a shotgun metagenomics analysis involving patients with AMD and healthy controls, Zinkernagel et al. observed that the AMD group exhibited a higher ratio of *Firmicutes* to *Bacteroidetes*, a pattern commonly linked to obesity. They also noted a higher abundance of the class

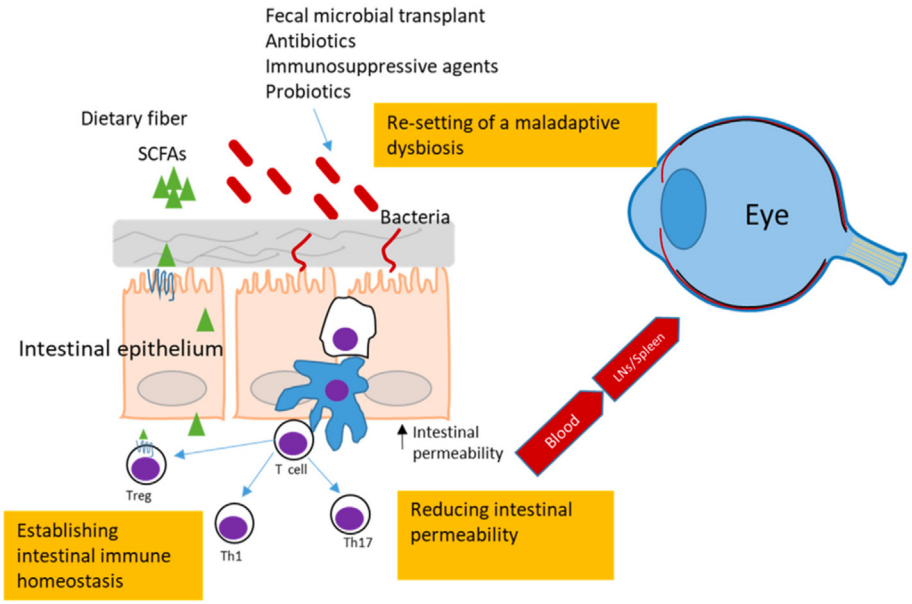

Fig. 4. Targeting the intestinal microbiota to treat uveitis.[56]
Various approaches can be considered, from re-establishing intestinal immune homeostasis by increasing Tregs, reducing intestinal permeability, or by re-setting a maladaptive dysbiosis with various strategies (fecal microbial transplant, antibiotics, immunosuppressive agents, probiotics) to reduce inflammation via multiple mechanisms. Tregs, regulatory T cells.

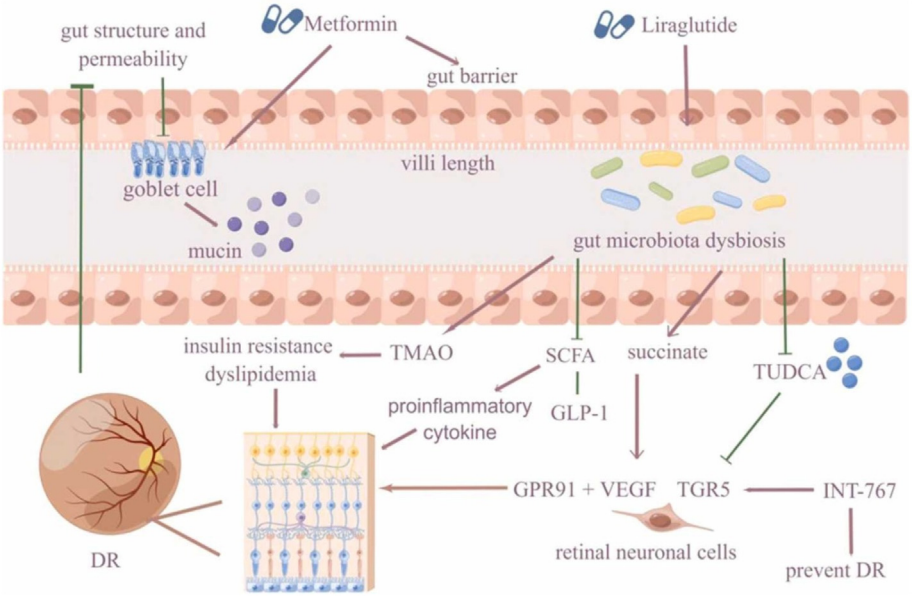

Fig. 5. The role of gut microbiota in the pathogenesis of DR.[63]
Dysbiosis of GM can lead to the increase of gut permeability, which eventually resulting microbial translocation and microbiota-derived metabolites into vein. Subsequently, the progression of DR is promoted via multiple mechanisms. The binding of VEGF and GPR91 may be directly involved in the pathogenesis of DR. In addition, increased TMAO may induce insulin resistance and dyslipidemia, eventually leading to DR. Meanwhile, decreased SCFA may induce DR development by secreting more proinflammatory cytokines. At the same time, reduction of TUDCA decreased TGR5, which collaboratively with INT-767 to prevent DR. DR, diabetic retinopathy; GM, gut microbiota; GPR91, G protein-coupled receptors 91; SCFAs, short-chain fatty acids; TMAO, trimethylamine-N-oxide; TUDAC, tauroursodeoxycholic acid; VEGF, vascular endothelial growth factor.

Negativicutes in AMD patients, while healthy individuals showed greater prevalence of the genus *Oscillibacter* and various *Bacteroides* species.[71,72] In another study, the class *Negativicutes*, identified as a candidate biomarker for AMD, showed a positive correlation with a specific SNP in the complement factor H (CFH) gene. Recognized as a major genetic risk factor for AMD, SNPs within the CFH gene can lead to over-activation of the complement system in the eye. This over-activation results in chronic low-grade inflammation, ultimately causing impairment of the RPE.[73,74] Changes in GM function in patients with AMD in contrast to healthy controls were also observed in some research, potentially linked to AMD development.[71]

3.3.2.3. Central serous chorioretinopathy. Typically characterized as self-limited retinopathy, central serous chorioretinopathy (CSCR) primarily affects males in their 20s–50s who might experience acute or sub-acute central vision loss or distortion. Although most acute CSCR cases resolve spontaneously within three months, it's worth noting that the recurrence rate can be significantly high, potentially reaching 31%.[75,76]

It is currently believed that CSCR results from hyperpermeable choroidal capillaries, which leads to neurosensory retina detachment, along with retinal pigment dysfunction. It has several risk factors, including high levels of endogenous cortisol and exposure to steroids, increased sympathetic activity, *Helicobacter pylori* infection, etc.[77] A study has suggested that disruptions in the GM can affect stress by modulating the endocrine system.[78] Consequently, GM alterations might impact stress hormone levels implicated in the development of CSCR. Furthermore, other research has identified microbial functional changes in pathways related to energy generation and fatty acid metabolism in CSCR patients, which may affect retinal homeostasis.[79]

3.4. Eye disease associated with systemic disease

3.4.1. Grave's ophthalmopathy

Grave's ophthalmopathy (GO), commonly referred to as thyroid eye disease, is an autoimmune inflammatory condition affecting the orbital and periorbital tissues, which primarily occurs in patients diagnosed with Grave's disease (GD).[80] As a prevalent disorder, GD impacts around 2% of women and 0.2% of men worldwide, with recent studies highlighting its association with GM dysbiosis,[81–83] and GO has similarly been linked to alterations of GM.[84,85]

Numerous clinical investigations have consistently reported significant changes in the GM composition of GD/GO patients compared to healthy controls, with prominent shifts in the abundance of *Prevotellaceae* and *Veillonellaceae* at the family level, and *Lactobacillus* at the genus level.[85] Furthermore, various GM-related enrichment metabolic pathways, including nucleotide and energy metabolism, as well as enzyme family, are disrupted in individuals with GD/GO. Interestingly, the GM in patients with GO also differs from that observed in GD patients without ophthalmopathy, indicating that GM may influence the severity of GD.[84] In vivo experiments have provided further evidence linking GM dysbiosis to the development of GD/GO by demonstrating that experimental animal models of GD/GO, derived from the same mouse strain but housed in different animal facilities, or from different mouse strains within the same facility, exhibit varying clinical manifestations.[85–87] Additionally, manipulating the GM in these GD/GO mouse models – via interventions such as antibiotic vancomycin, probiotics supplementary, or fecal microbiota transplantation from GD/GO patients – has been shown to affect the onset and progression of GD/GO.[87,88]

While the main pathogenic mechanism of GD is attributed to the production of autoantibodies against the thyroid-stimulating hormone receptor (TSHR), which act as agonists and trigger excessive thyroid hormone secretion, the resulting release from pituitary regulation. These autoantibodies can also target orbital fibroblasts, stimulating their differentiation into adipocytes, leading to the expansion of fat cells and muscle tissues and the compression of veins in the orbit, which ultimately contributes to the clinical features of GO.[80,81] Despite these insights, the full etiology of GD/GO remains unclear. It is generally believed to result from a combination of strong genetic susceptibility and environmental factors in individuals with an inherently vulnerable immune system. As evidenced by clinical research and experimental animal studies above, GM dysbiosis has been proposed as a critical factor in the pathogenesis of GD/GO, with two primary mechanisms suggested: antigenic mimicry and the imbalance between Th17 and Treg cells.[85] Antigenic mimicry occurs when microbiota-derived molecules resemble autoantigens such as TSHR, triggering the production of antibodies that can target both thyroid cells and orbital fibroblasts. Pathogenic microorganisms, including *Yersinia enterocolitica*, *Helicobacter pylori*, and *Prevotella*, are believed to play a role in this process. In addition, GM dysbiosis may lead to the depletion of beneficial bacteria and a reduction in anti-inflammatory metabolites, such as SCFAs, which are known to support Treg differentiation. Moreover, segmented filamentous bacteria are known to promote Th17 cell differentiation, and an imbalance between Th17 and Treg

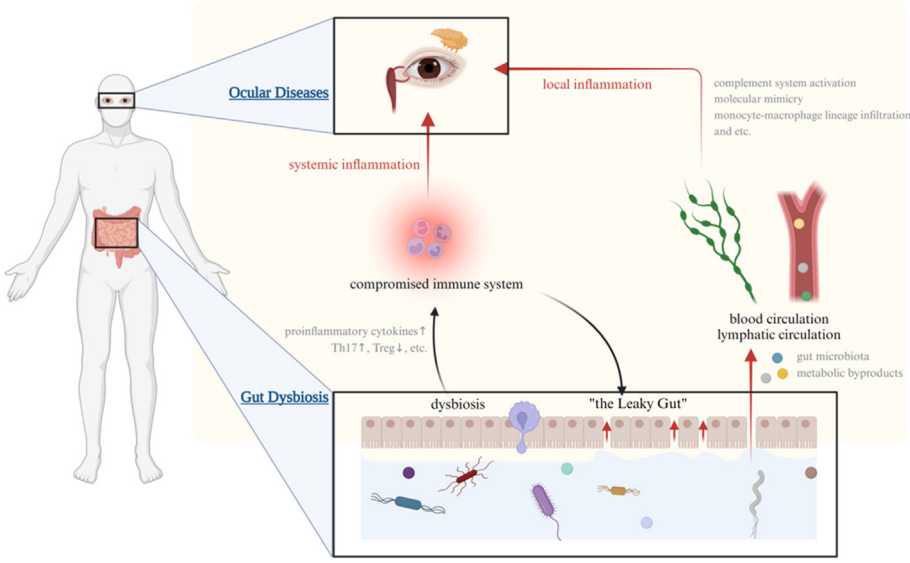

Fig. 6. The Gut-Eye Axis.
Two mechanisms are proposed to explain the link between GM and ocular diseases. GM dysbiosis disrupts immune homeostasis, inducing systemic inflammation via proinflammatory cytokines and Th17/Treg imbalance, which may contribute to ocular tissue damage. Additionally, increased gut barrier permeability ("the leaky gut") facilitates the translocation of microbial products such as LPS into circulation, potentially reaching the eye and triggering localized inflammation through complement activation, molecular mimicry, and monocyte-macrophage. GM, gut microbiota; LPS, lipopolysaccharides; Tregs, regulatory T cells. (created with BioRender.com.).

populations could further exacerbate the progression of GD/GO. Various therapeutic approaches aimed at modulating the microbiota, such as the use of antibiotics, probiotics, and dietary interventions, have been actively explored in preclinical and clinical settings.[87,89] However, the current evidence on their effects in GD/GO patients remains limited, necessitating further investigation to clarify the molecular pathways connecting gut and thyroid functions and their impact on orbital autoimmune responses.

3.5. Gut-eye axis

Recent studies investigating various ocular disorders have yielded compelling evidence in favor of the "gut-eye axis". Two possible mechanisms have been postulated to elucidate the interconnections between GM and ophthalmic pathologies (Fig. 6.). Perturbations in the GM compromise the immune response, leading to systemic inflammatory responses.[90,91] This process is predominantly mediated through the upregulation of proinflammatory cytokines and a disruption in the balance between Th17 and regulatory T cells, among other factors.[92] Such systemic inflammation may precipitate tissue damage, potentially contributing to the pathogenesis of diverse ailments, including those affecting ocular structures.[93] Intricately linked to this phenomenon is the consequence of immune dysregulation resulting from dysbiosis. This imbalance can lead to reduced barrier function with increased intestinal permeability, often referred to as a "leaky gut".[94–96] This condition facilitates the translocation of GM and their metabolic byproducts, such as LPS, into the circulatory or mesenteric lymphatic systems.[97] These agents may subsequently migrate to immunologically privileged regions like the eye, where they initiate localized inflammatory cascades through multiple pathways. These mechanisms encompass, but are not limited to, complement system activation, molecular mimicry, and the infiltration of cells from the monocyte-macrophage lineage.[79]

This conceptual framework provides valuable insights into the intricate relationship between gastrointestinal microbiota and ocular well-being. It underscores the far-reaching ramifications of gut dysbiosis on visual function and ocular tissue homeostasis, emphasizing the paramount importance of maintaining a balanced GM for overall ocular well-being. Elucidating these interconnected mechanisms may pave the way for innovative therapeutic approaches targeting the gut-eye axis in the management of ocular diseases.

4. Conclusions

In recent years, growing interest has emerged in probing the interconnected relationship between the gastrointestinal system and the ocular health. Traditionally, the gut has been viewed primarily through the lens of nutrient metabolism, but we now know that it harbors a vast and diverse community of microorganisms that engage in a symbiotic relationship with the immune system. This mutually beneficial interaction is instrumental in maintaining gastrointestinal homeostasis and modulating inflammatory processes. Consequently, disruptions in this delicate balance of the GM have been correlated with a range of health issues, potentially extending to the eyes.

While many research have tried to investigate the connection between GM and eye, the specific mechanisms connecting these two systems remain somewhat unclear. How exactly the gut's microbial inhabitants and their metabolic products influence the onset or progression of ocular diseases is still a subject of investigation. That said, this review aims to bring together recent findings on ocular diseases, offering insights into the potential pathogenic pathways while also outlining the broader principles that shape what is now being called the "gut-eye axis" (Fig. 6.).

Although more investigations are essential to validate these mechanisms, the concept of the "gut-eye axis" opens up exciting new possibilities for treatments. These may involve strategies like adjusting gut microbial populations through dietary changes, short-chain fatty acid supplements, probiotics, selective antimicrobial use, or even fecal microbiota transplantation.[98] In addition to the microorganism in the gastrointestinal tract, research has demonstrated that the microbiota in other regions of the human body, such as the ocular surface, skin, and nasal cavities, also plays a critical role in maintaining eye health.[99,100] As our understanding of this intricate interplay between the microbiota and ocular diseases deepens, novel treatment modalities are expected to emerge, potentially revolutionizing the management of ocular diseases!

Study approval

Not applicable.

Author contributions

The authors confirm contribution to the paper as follows: Conception and design of study: NH, PY; Drafting the manuscript: WZ, MS; All authors reviewed the results and approved the final version of the manuscript.

Funding

This work was supported by the Natural Science Foundation of Zhejiang Province (LTGY24H120002).

Declaration of competing interest

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.

Acknowledgments

Thanks to all the peer reviewers for their opinions and suggestions.

Abbreviations

ACE2	angiotensin-converting enzyme 2
AMD	age-related macular degeneration
BCAA	branched-chain amino acids
CFH	complement factor H
CSCR	central serous chorioretinopathy
DED	dry eye disease
DM	diabetes mellitus
DR	diabetic retinopathy
EAU	experimental autoimmune uveitis
GD	Grave's disease
GM	gut microbiota
GO	Grave's ophthalmopathy
GPCR	G protein-coupled receptor
GPR91	G protein-coupled receptors 91
HSPs	heat shock proteins
IOP	intraocular pressure
LPS	lipopolysaccharides
MHPG	3-Methoxy-4-hydroxyphenylglycol
RGCs	retinal ganglion cells
RPE	retinal pigment epithelium
SCFA	short-chain fatty acids
TLR4	Toll-like receptor 4
TMA	trimethylamine
TMAO	trimethylamine-N-oxide
TSHR	thyroid-stimulating hormone receptor
TUDCA	tauroursodeoxycholic acid
VEGF	vascular endothelial growth factor

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