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Gut Microbes and Eye Disease

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Abstract

Microbial symbionts in the gut are increasingly recognized as having important effects on health and disease, but have only recently begun to be linked to diseases of the eye. We review current research on the intestinal microbiota's relationship to ocular disease, focusing on autoimmune uveitis, diabetic retinopathy, age-related macular degeneration and primary open angle glaucoma. We discuss findings and limitations of this exciting new area of ophthalmology research and explore possible future disease-modifying treatments.

Keywords

gut microbiome; glaucoma; age-related macular degeneration; diabetic retinopathy; autoimmune uveitis

Introduction

The human gut microbiota comprises an estimated 4×10^{13} bacteria[1] and other microorganisms[2] which play important reciprocally regulated roles in host digestion and absorption,[3] immune function,[4,5] vitamin and amino acid synthesis,[6] and drug metabolism.[7,8] Dysbiosis of the gut has well-supported ties to a host of human diseases, including cardiovascular disease,[9,10] metabolic syndrome and diabetes,[11,12] gastrointestinal and systemic autoimmune disease,[13] and cancer, as well as chronic and inflammatory diseases of the eye.[14] Until recently, the effects of microbiota on ophthalmic disease have been less studied than gastrointestinal and systemic diseases. While there is ample research on the relationship between microbiota and systemic conditions (for example, high blood pressure and diabetes) which affect the incidence and progression of eye disease, clinical and basic research on ocular disease specifically has accelerated only in the last few years. Recent evidence aimed at elucidating the relationship between the human eye and gut microbiota supports the presence of a gut-eye axis, *i.e.* effects

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Author contributions

PD and ED performed the literature review and wrote the paper. JC and QL designed the study and edited the paper. All authors approved the final version of the manuscript.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

of gut microorganism-derived mediators on structures within the eye (Fig. 1).[15,16] In support of the gut-eye axis, many studies have uncovered an association between alterations in gut microbial composition and ocular disease, as well as possible therapeutic effects of manipulating the microbiome with dietary interventions and antibiotic treatment. This review will focus on gut microbiota and intraocular diseases; we will review current research on association of gut microbiota with autoimmune uveitis, diabetic retinopathy, age-related macular degeneration (AMD), and primary open-angle glaucoma (POAG).

Autoimmune uveitis

Uveitis is a disease characterized by inflammation of the uvea, a structure in the eye composed of the choroid, iris, and ciliary body, as well as the neural retina; clinical manifestations vary with the involved anatomy but include redness, pain, photophobia, and loss of visual acuity. Uveitis affects 115.3 per 100,000 people in the United States, with a similar lifetime incidence worldwide, and is reportedly more common in females than in males.[17,18] Inflammation in uveitis can be triggered through either non-infectious or infectious mechanisms, though this article will focus on non-infectious or autoimmune uveitis due to its well-studied relationship to gut microbial dysbiosis. Autoimmune uveitis may be isolated or associated with a wide range of systemic inflammatory conditions; it is a clinically and mechanistically heterogeneous group of diseases. We will discuss the association between gut microbial composition and uveitis and then review the hypothetical mechanisms by which gut dysbiosis may contribute to intraocular inflammation..

In studies on human fecal samples, gut microbial diversity was decreased in the uveitis condition; one study found differences in within-group (alpha) diversity[19] while another found differences in between-group (beta) diversity.[20] Principal component analysis of 16S rRNA sequences of gut microbes in uveitis patients and healthy controls found significantly divergent bacterial communities. Closer analysis of microbial composition found decreased abundance of the genera *Ruminococcus* and *Oscillospora* in uveitis patients,[20] while another study did not find a significant difference in gut microbiota composition between uveitis patients and controls.[19] In one study, the genera *Faecalibacterium*, *Bacteroides*, *Clostridium*, and *Lachnospira*, which are known for their anti-inflammatory properties, were found to be reduced in uveitis patients and *Prevotella*, a pro-inflammatory genus, to be enriched.[20] These studies were unable to ascertain if observed changes in gut microbial composition were responsible for or a result of disease. Interestingly, gas chromatography-mass spectrometry analysis of fecal samples from anterior acute uveitis patients yielded a significant difference in fecal metabolic phenotype compared to healthy controls.[19] These results suggest that even if changes in microbial composition are undetectable or inconsistent, there could be functional differences in the guts of uveitis patients contributing to disease.

The results of these studies, as well as an extensive literature on associations between gut microbiota and systemic autoimmune diseases linked to uveitis,[13] raise the question of the mechanism by which gut bacteria may affect the eye. There are four proposed mechanisms implicating gut microbial dysbiosis in the pathogenesis of autoimmune uveitis. These mechanisms are microbial metabolites, destruction of the intestinal barrier, imbalance

of intestinal immune homeostasis, and antigenic mimicry.[21] In the first hypothesized mechanism, microbes in the gut are capable of producing a number of metabolites, including butyric acid and short-chain fatty acids, which have protective properties in inflammation. Alterations in the microbial composition of the gut can decrease levels of beneficial microbial metabolites, exacerbating inflammation in uveitis. In the second mechanism, a weakened intestinal barrier due to dysbiosis can lead to leakage of pathogenic products of microbes into the systemic circulation. These products such as lipopolysaccharides (LPS) could land in the uvea and elicit an immune response, leading to uveitis.[22] In the third mechanism, an imbalance of T helper 17 (Th17) and T regulatory (Treg) cells results in overproduction of IL-17, stimulating an inflammatory pathway and promoting uveitis.[23,24] The last mechanism involves antigenic mimicry whereby T cells capable of recognizing self-antigens in the uvea are activated in the gut by microbial peptides. One study found that T cells activated by an experimental autoimmune mouse model's intestinal extracts induced autoimmune uveitis in naïve wild-type mice, supporting antigenic mimicry as an inciting role in autoimmune uveitis[25]. It is likely that more than one of these hypothesized mechanisms are at play in the pathogenesis of autoimmune uveitis as they are not mutually exclusive and reflect a complex interplay of immune cells and gut microbial dysbiosis.

Diabetic retinopathy

Diabetic retinopathy (DR) is one of the cardinal manifestations of microvascular compromise in diabetes mellitus. DR is divided into non-proliferative DR, proliferative DR, and diabetic macular edema. Retinal changes associated with uncontrolled diabetes are typically asymptomatic for years until late stages, when visual compromise may progress rapidly due to vitreous hemorrhage, tractional detachment, secondary glaucoma, or macular edema. For this reason and because of the high prevalence of diabetes, DR is the leading cause of blindness among working adults in developed countries, and is associated with significant healthcare costs.[26–28]. Duration and severity of hyperglycemia as well as high blood pressure are the primary risk factors for development and progression of DR, but patient-specific factors also exist—some people never develop DR despite years of hyperglycemia. Many studies have demonstrated effects of gut microbiota on diabetes,[12] but relatively few have investigated effects specifically on diabetic retinopathy. In this section, we will discuss experimental evidence investigating the relationship between the gut microbiota and DR.

Several studies have investigated the differences in gut microbial composition between diabetic patients with and without DR; the first, using traditional selective culture media techniques, found no significant differences,[29] while the second, using 16S rRNA gene sequencing from 25 patients with diabetes, 28 patients with DR and 30 age- and sex-matched healthy controls,[30] found differences at the genus level, with DR patients' stool having reduced abundance of both anti-inflammatory and pathogenic genera. More than half of patients in the diabetes cohort of this study had a new (<4 month) diagnosis, whereas the DR patients all had years-long history of diabetes. Treatment with metformin, for example, has been shown to have predictable effects on the gut microbiome that may form part of its mechanism of action.[31] In an effort to determine if DR-associated microbiota changes

exist independently of those induced by years of diabetes or its treatment, Khan *et al.* performed 16S rRNA sequencing on fecal swabs from 37 patients with sight-threatening diabetic retinopathy and 21 matched controls, all with greater than 10 years' history of diabetes; they found no significant differences in abundance of measured taxa, though the ratio of Bacteroidetes to Firmicutes was found to be significantly different between patients and controls. In a similar vein, Huang *et al.* evaluated 25 patients with DR, 25 patients with T2DM without DR matched for duration of disease, and 25 healthy controls.[32] Significant differences were found between healthy controls and the DM and DR groups, but few differences were found between DM and DR groups. More research is needed to validate these results and determine if gut microbiota affect DR independent of DM status.

In animal models, several studies have discovered a relationship between a favorable gut microbial environment and improved DR outcomes in diabetic rodent models.[33,34] Intermittent fasting (IF) was found to both induce a shift from bacterial species of Bacteroidetes to Firmicutes in the gut, to decrease the activation of retinal microglia and infiltration of peripheral immune cells into the retina, and to improve overall survival in a type 2 diabetic mouse model.[33] Species belonging to Firmicutes can metabolize primary bile acids to secondary bile acids such as tauroursodeoxycholic acid (TUDCA), a compound found to have protective properties in rat retinal neurons.[34,35] The authors hypothesized that an increased proportion of Firmicutes in the gut could improve DR outcomes through the protective effects of TUDCA, a byproduct of Firmicutes bile acid metabolism. The mechanism by which TUDCA improves DR outcomes was explored in experiments on rat retinas exposed to a diabetic condition.[34–36] TUDCA was found to decrease expression of immune mediators and angiogenic factors such as nitric oxide synthase, ICAM-1, NF- κ B p65, and VEGF in diabetic mouse models. In cultured rat retinal neurons exposed to elevated glucose concentrations, TUDCA decreased cell death by attenuating the release of apoptosis-inducing factor (AIF) in mitochondria and reducing oxidative damage.[34] TGR5, a receptor of TUDCA, has been shown to play a role in DR pathology in mouse models.[37] These results suggest that TUDCA may play a number of roles in preventing DR progression such as alleviating inflammation and preventing retinal cell death in DR.

Overall, these studies also propose that dietary modifications such as IF and administration of TUDCA could be used as treatments for DR and other retinal diseases. IF was found to shift the gut microbial community towards larger proportions of *Firmicutes*, thus increasing bile acid metabolism and TUDCA production.[33] Future research points towards elucidating a more specific gut microbial profile associated with DR and tailoring treatments of retinal diseases involving TUDCA.[38]

Age-related macular degeneration

Age-related macular degeneration (AMD), the leading cause of adult blindness in high-income countries, is a multifactorial disease with incompletely understood pathogenesis, but epidemiologic studies have implicated genetic differences, innate immunity,[39,40] inflammatory markers,[41] diet,[42,43] and specific vitamin[44] intake in AMD incidence and progression. Given that microbiota shape both host immune response and metabolism, [45,46] and that diet shapes gut microbial communities,[47] recently researchers have

sought to find effects of microbiota on AMD. Two case-control studies from the same group found that the feces of AMD patients were enriched in bacterial taxa associated with high-fat diet and inflammation, such as *Anaerotruncus*, and reduced in *Bacteroides* spp., which are associated with protection from autoimmune disease and fermentation of indigestible carbohydrates.[48,49] The authors found associations between the complement system and gut microbiome changes in C3^{-/-} mice--a genetic background that negatively affects aged retinas—including increases in Firmicutes-to-Bacteroidetes ratio and the abundance of order Clostridiales. In humans, similar gut microbiome changes were correlated with single nucleotide polymorphisms (SNPs) in the complement factor H gene, suggesting a relationship between complement deficiency, specific gut microbiome changes, and AMD. Metabolic pathway inferences suggested that gut bacteria of AMD patients have reduced fatty acid elongation and increased L-alanine fermentation, glutamate degradation and arginine biosynthesis, which may plausibly affect retinal health.[50,51] Corroborating these studies, Andriessen and coworkers found that wild-type mice fed a high-fat diet have both greater choroidal neovascularization in response to experimental laser injury and an increased ratio of gut bacteria in phylum Firmicutes at the expense of Bacteroidetes, as well as increased gut dye permeability and measures of systemic and choroidal inflammation. [52] Normalization of gut bacterial phyla via fecal transplant restored normal-diet levels of laser-induced choroidal neovascularization, regardless of diet, indicating that gut microbiota are a necessary intermediary for diet-induced increases in choroidal angiogenesis. Rowan and co-workers found that mice fed a high-glycemic index diet develop features similar to dry AMD, including retinal pigmented epithelium depigmentation and atrophy, as well as changes in gut bacteria. As in prior studies, both the high-glycemic-index diet and worse retinal pathology were associated with increased abundance of phylum Firmicutes (including Clostridia) and reduced abundance of phylum Bacteroidetes; the authors identified reduced bacteria-derived serotonin as a diet-independent factor in retinal damage.[53] It is challenging to generalize to human disease from animal models of AMD since only the primate eye has a macula,[54] but these results suggest that a shift in gut microbes may be a factor in AMD pathogenesis. Mechanisms may include increased systemic inflammation by permeation of antigens through a compromised intestinal mucosal barrier, bacterial metabolism of lipids or neurotransmitters, or bioavailability of dietary vitamins or micronutrients. This work merits further validation in human patients with AMD.

Finally, a role for oral dysbiosis in AMD has also been investigated in two case-control studies. In a cohort of 311 mixed AMD patients and 421 healthy controls in Singapore, Ho and co-workers found that pharyngeal microbiota were similar in overall structure and diversity between AMD and control patients, with differences in the abundance of specific genera.[55] *Prevotella* spp. was found to be relatively reduced, and *Gemella* and *Streptococcus* spp. relatively enriched, in AMD; this difference was found to be larger and *Leptotrichia* spp. also reduced when stratifying for late AMD. *Prevotella* spp. being less common in AMD is surprising, since members of genus cause periodontal disease[56] and are associated with autoimmune arthritis.[57] In a small case-control study of oral and nasal microbiota, Rullo and co-workers found large differences in many taxonomic units of bacteria, including some linked to atherosclerosis, and recapitulated the prior study's finding

of enrichment of *Gemella* spp. in AMD.[58] Both studies suffered from a lack of baseline matching between the AMD and control cohorts. More work needs to be done to establish a role for oral or nasal microbiota in AMD.

In summary, multiple studies in mice and humans have identified changes in gut bacteria, specifically an increased fecal Firmicutes:Bacteroidetes ratio, as a possible factor in both neovascular and dry AMD. More work needs to be done to validate these findings in wider groups of patients, and to elucidate whether these changes are a diet-dependent. Studies of oral microbiota in AMD have not produced convincing evidence of an association.

Glaucoma

Glaucoma is a group of neurodegenerative diseases of the optic nerve head associated with increased intraocular pressure (IOP); together they are the world's leading cause of irreversible blindness. Many theories have been promulgated to explain the observed patterns of neurodegeneration in patients with glaucoma and their relationship with elevated IOP, but none have prevailed. Since autoantibodies to retinal[59] and optic nerve antigens[60] were discovered in glaucoma patients in the 1990's, autoimmunity has been hypothesized to play various roles (including protective ones) in glaucomatous neurodegeneration. In addition to circulating antibodies, abnormal T-cell repertoires have been identified in glaucoma patients.[61] Recently, work on the effects of microbiota on the intraocular pathology of glaucoma has accelerated, often focused on autoimmune or inflammatory aspects. Some of this work on glaucoma has been reviewed previously,[14,62–64] and may be divided into studies of oral microbiota and studies of gut microbiota, including gastric *H. pylori* colonization and gut microbiota-mediated autoimmunity to heat shock proteins. The one study that does not fit into these categories, interestingly, performed stool 16S RNA sequencing and serum GC-MS metabolomics to explore differences in microbiota-mediated metabolism in 30 POAG and 30 matched controls.[65] The authors found that stool samples of POAG patients were relatively enriched in *E. coli* and Prevotellaceae and relatively reduced in *Bacteroides plebeius* and *Megamonas spp* and linked these taxa to specific metabolites that may play a role in glaucoma pathogenesis.

Based on a well-tread hypothesis that innate or adaptive immune response to the oral biofilm may mediate neurodegenerative changes,[66] as well as evidence of a role for both complement cascade[67] and the TLR4 receptor[68,69] in glaucoma, several authors have pursued a link between oral microbiota and glaucoma. Promising initial results[69] of almost 2-fold differences in oral bacterial counts in POAG patients vs matched controls were not replicated in a prospective follow-up study.[70] Prospective data from the Health Professionals Follow-up Study[71] and a large retrospective cohort study in Taiwan[72] found inconsistent connections between oral health and risk of glaucoma, with the former study finding that only recent tooth loss alone or tooth loss and periodontal disease was associated with POAG, while the second study found that only periodontal disease was associated with POAG. The link between oral health and glaucoma remains unclear.

Glaucoma was first associated with gut microbiota in 2000, when histologically confirmed gastric *H. pylori* infection was found in 88% of glaucoma patients vs 47% of anemic controls by Kountouras and co-workers.[73] Subsequent studies using serology and/or

[¹³C]urea breath testing found mixed results,[74] but the most recent meta-analyses overall found evidence of an association between active *H. pylori* infection and POAG.[75,76] *H. pylori* infection has been hypothesized to worsen glaucoma via systemic inflammation and increased vasoactive and reactive oxygen species[68] or antibody-dependent responses to cross-reactive ocular antigens.[77] One study even found *H. pylori* coccoid forms in trabecular and iris specimens from POAG patients,[78] a surprising but likely artifactual finding given that *H. pylori* is an obligate colonizer of gastric mucosa.[79] Successful eradication of *H. pylori* infection in small trials of POAG patients has been found to improve both IOP[80] and visual fields,[81] but eradication in patients with peptic ulcer disease without glaucoma, however, did not change the risk of developing POAG.[82] There remains insufficient evidence to determine if a causative relationship exists, or if the observed association arises from shared susceptibility; subsequent studies on gut microbiota in POAG have taken the observed association with *H. pylori* infection as an indication that intestinal dysbiosis is a risk factor for both diseases.[64]

The third and final line of investigation into microbiota and glaucoma concerns gut microbiota-mediated immune responses to heat shock proteins (HSPs), which are a large family of molecular chaperones that play diverse roles in signaling and stress response. Autoantibodies to small HSPs were identified in the serum of patients with POAG in 1998,[83] quickly followed by attempts to determine their role in glaucoma pathogenesis. [84,85] HSPs are both immunogenic and highly conserved, and loss of tolerance to commensal bacterial HSP homologs has been proposed to contribute to many autoimmune and neurodegenerative diseases.[86] In 2018, Chen and co-workers provided compelling evidence for this model, showing that transient IOP elevation in mice causes HSP-specific T-cells to infiltrate the retina and contribute to RGC and axon loss, and that this process is attenuated in a low-diversity gnotobiotic mouse model and abolished in germ-free mice. [87] They then generated a germ-free version of the DBA/2J mouse model of hereditary glaucoma and found that while those animals developed the expected elevation in IOP, they had no RGC and minimal axon loss by 12 months of age. Furthermore, the authors identified HSP-reactive T-cells in the peripheral blood of glaucomatous patients but not healthy patients or those with other diseases. The authors integrated these findings into a two-hit model of glaucoma pathogenesis: first, exposure to commensal bacteria in some way primes a T-cell response against self-antigens; second, elevated IOP (or another insult) allows T-cell infiltration into the retina and stimulates retinal cells to express stress factors that become the target of a sustained immune response that drives neurodegeneration and vision loss. These striking results raise several questions. First, *Rag1*^{-/-} and *TCRβ*^{-/-} mice subjected to transient IOP elevation still developed RGC and axon loss, while otherwise immunocompetent GF mice did not, indicating that classical αβ T-cell responses are not responsible for the bulk of neurodegeneration. Second, the timing and nature of immune priming by gut microbiota, or how they may differ between individuals with glaucoma, remains unknown. More work remains to be done to elucidate other roles for microbiota in glaucoma, and to characterize differences in microbiota among patients with glaucomatous disease.

In summary, a real association exists between POAG and active *H. pylori* infection, but it remains unclear if eradication provides any ocular benefit. Evidence in mice indicates

that intestinal dysbiosis may contribute to glaucoma progression by inducing immune intolerance to cross-reactive retinal antigens, but these findings will need to be corroborated in humans. Small observational studies have found inconsistent associations between POAG and periodontal disease.

Concluding remarks

Many of these studies have significant limitations. Because gut and other microbiota are sensitive to diet, environment, and other aspects of the life history, observational studies cannot control for all possible confounders. Studies may be inadvertently using gut microbiota as a proxy for socioeconomic status, diet quality, or environmental exposures. A standardized approach has been proposed, using parallel clinical and translational research in both patients and germ-free mice, to better establish causality in microbiota research.[45] Successful trials are also a nice way to establish causation, but interventions to modify gut flora lag behind the techniques used to characterize them in sophistication and subtlety (see Table 1). Probiotics and prebiotics have mixed evidence of efficacy[88,89] and are difficult to standardize. Heterologous fecal microbiota transplantation has strong evidence of efficacy in certain conditions (e.g. recurrent *Clostridoides difficile* infection),[90] but is even harder to standardize, with high variance in outcomes based on donor stool quality.[91] Administration of antibiotics in the absence of specific pathogens can only reduce diversity and is not safe. On the horizon are several emerging methods that may provide new ways to leverage discoveries about microbial symbionts in disease. Administering postbiotics, *i.e.* microbe-derived products rather than the live organism, may avoid bioavailability issues and be easier to standardize; this approach was discussed above in the context of diabetic retinopathy. Microbial strains have been engineered both to efficiently colonize the gut and to express disease-modifying pathways.[92] Finally, bacteriophage therapy[93] or CRISPR-Cas9-based methods[94] may allow the microbiome to be edited *in situ* without needing to introduce new species.

Now research on gut microbiota and ocular health faces an exciting prospect. Many connections have been uncovered between gut microbiota and several chronic eye diseases, but much work remains to be done to elucidate these connections with increasing specificity and certainty. Most importantly, prospective studies need to determine if intervening on gut dysbiosis has a meaningful effect on the prognosis of ocular diseases. Some of these mechanisms may prove to be the foundation of new treatments, and basic and clinical research will need to evolve together to realize the potential of these discoveries in this rapidly changing field.

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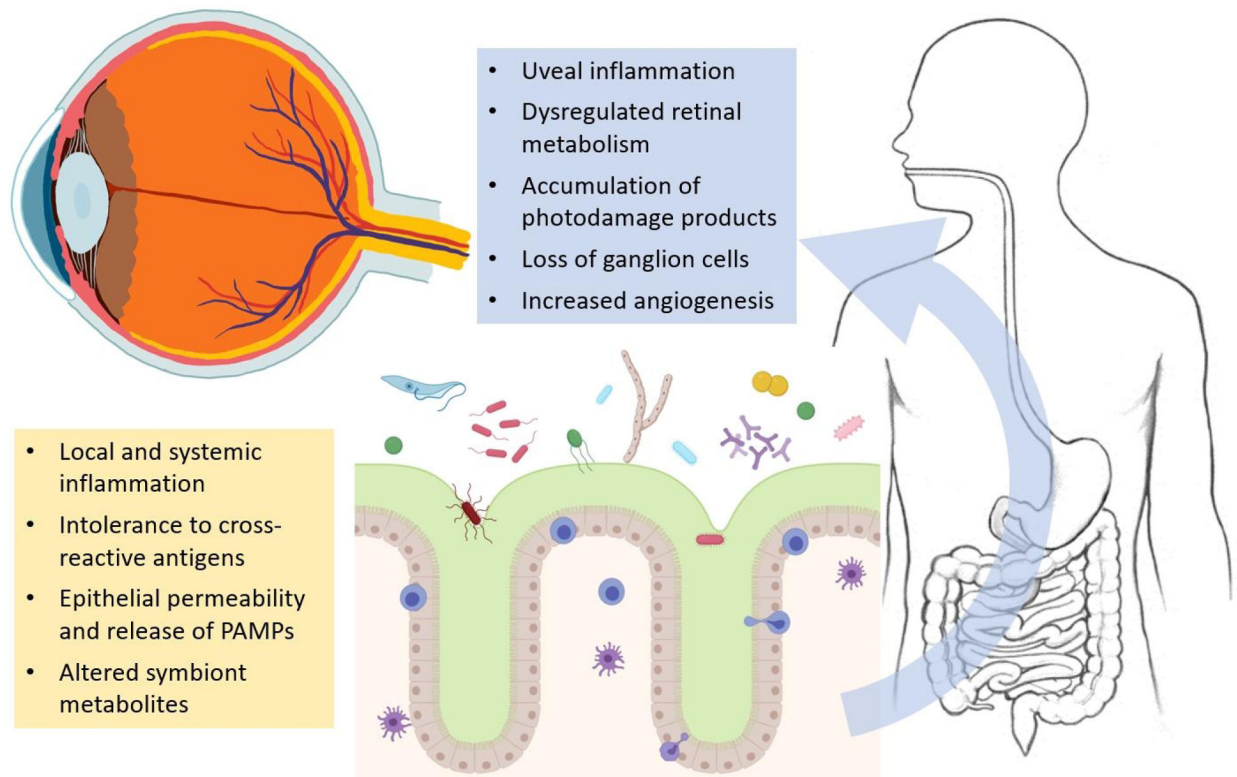


Fig. 1. Downstream direct and indirect effects of gut dysbiosis on the eye. Maladaptive changes in the microbial communities overlying oral/intestinal mucosa may be induced by diet, environmental exposures, illness or drugs, causing diverse effects on eye physiology.

Table 1.

Interventions proposed to alter gut microbes for disease modification.

Intervention	Strengths	Limitations
Antibiotics ⁴⁵	Effective in suppressing susceptible organisms	Unlikely to promote the growth of desirable organisms, reduces diversity, contributes to antimicrobial resistance
Probiotics/prebiotics ^{88,89}	Widely used, safe	Most preparations fail to colonize the intestines, hard to standardize
Fecal microbiota transplantation ^{90,91}	Proven effective in some conditions	Donor-dependent, resource intensive
“Postbiotics” (bacterial products) ^{34,35,45}	Easier to standardize	Unclear efficacy
Engineered bacterial strains ⁹²	Possibly more reliable colonization, controllable	Complex, untested
Phage/CRISPR-Cas9 modification ^{93,94}	Targeted introduction or ablation of specific genes or pathways <i>in situ</i>	Complex, untested