Review

Role of intestinal microbiome in the pathogenesis of age-related macular degeneration

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ABSTRACT

Background: The microbiome is strongly linked to many extra-intestinal disorders. Gut commensal microbiota, in particular, plays an active role in human immune and intestinal homeostasis. Complex interactions of the microbiota with host genetics and other underlying factors lead to intestinal dysbiosis, which is thought to be linked to ocular inflammatory diseases. Thus, the aim of this review is to analyze the role of intestinal microbiome in age-related macular degeneration (AMD).

Methods: A thorough literature search was performed using PubMed/MEDLINE, limited to English language publications, from January 2004 to March 2020. An additional search was made employing Google Scholar to complete the collected data as per the above-mentioned time-line and language limitations. The main keywords used included age-related macular degeneration, microbiome, dysbiosis, autoimmunity, gut microbiota, epigenetics, immune-mediated inflammatory diseases, and gut-retina axis.

Results: Recent studies have proposed the role of intestinal microbiota in the pathogenesis of AMD. Changes in the microbiome have been shown to trigger several ocular inflammatory processes. There is increasing evidence demonstrating that intestinal microbial imbalance may play an important role in the pathogenesis of AMD.

Conclusions: This review summarizes how alterations in the intestinal microbiota can be associated with the pathogenesis of AMD and how new therapeutic modalities can be designed to target this microbiome to limit the severe nature of this disease. Future advances in microbiome research may unveil a new era in understanding and managing AMD.

KEY WORDS

age-related macular degeneration, AMD, gastrointestinal microbiome, gut microbiome, gut flora, dysbiosis

INTRODUCTION

A microbiome consists of microorganisms coexisting symbiotically within the human body and their genetic material [1, 2]. Most of these microorganisms reside in the small and large intestines. The gastrointestinal (GI) tract has been found to contribute to 70% of our body's immune system. Every individual has a specific meshwork of microbiota that is predetermined by its own DNA, thus making microbiota of each person unique. In the past, it was believed that these microorganisms were passive passengers in the human body. Nowadays, it

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is widely known that they play a very important role in early postnatal mucosal and systemic immunity, as well as contribute to homeostasis of the immune system. This has been revealed through experimental studies that associate the microbiome of the intestines to its control of both innate and adaptive immune responses. Intestinal microbiome dysbiosis, which is an imbalance between beneficial and harmful microbes of the intestinal tract, has been associated with various diseases, such as rheumatoid arthritis, cardiovascular disease, type 1 diabetes, multiple sclerosis, and spondyloarthritis [1, 2]. For example, some specific strains of segmented filamentous bacteria of the gut microbiota of rodents [3] and similar bacterial strains of human gut microbiota [3] have been found to regulate differentiation of colonic regulatory T cells (Tregs) and T helper cell 17 (Th17) in the gut. Pathogenic Th17 cells are strongly related to inflammatory diseases such as arthritis and non-infectious uveitis. However, differentiation of Tregs plays an important role in homeostasis of the immune system [1]. This differentiation is produced by specific strains of Clostridia and Bacteroides fragilis. Furthermore, short chain fatty acids (SCFAs) that result from the fermentation process of nutritional fibers or those derived from exogenous routes increase the predominance of Tregs in the intestines and also have a protective role against T-cell-mediated colitis [1]. Moreover, due to a specific balance between symbiosis of microorganisms in the gut, any differences in the intestinal barrier activity, reinforcement, or debilitation would increase intestinal permeability.

Thus, the aim of this review was to analyze the role of intestinal microbiome in age-related macular degeneration (AMD).

METHODS

A thorough literature search was performed using the PubMed/MEDLINE bibliographic database from January 2004 to March 2020. Papers in languages other than English were excluded. An additional search was performed employing Google Scholar to complete the collected items as per the above-mentioned time-line and language limitations. The main keywords used included 'age-related macular degeneration', 'microbiome', 'dysbiosis, autoimmunity', 'gut microbiota', 'epigenetics', 'immune-mediated inflammatory diseases', and 'gut-retina axis'.

RESULTS

A critical appraisal was conducted for papers published between 2004 and 2020, with special emphasis on studies published within the last five years. Table 1 summarizes the characteristics of articles related to the role of intestinal microbiome in the pathogenesis of AMD that are included in this review.

DISCUSSION

Microbiome Dysbiosis and Human Health

Numerous hypotheses on how gut microbiota can initiate an inflammatory process distal from the intestinal tract have been proposed. The first hypothesis is that differentiation in T-cell population leads to harmful intestinal bacteria, overcoming the beneficial ones. This results in an abnormal immune response, which increases immune regulatory cell types (e.g., Th17) and decreases immune regulatory cell types such as Tregs. Consequently, the activation threshold of Th17 cells decreases, and their numbers increase in different parts of the body. If the environment is ideal for bacterial growth, they can become pathogenic [4].

Another hypothesis is that stimulation of tissue-reactive T-cells by self-antigens and commensal peptides, through their cross-reactivity, leads to immune-mediated diseases [5]. Finally, another hypothesis states that dysbiosis may occur between different microbes in the intestines, leading to increased permeability of the intestinal barrier either for harmful bacteria or non-specific bacterial antigens. As they travel through the blood stream or the lymphatics, they can cause dysregulation of extra-intestinal acquired immune responses [6]. Several studies have also found a causative link between host genetics, HLA-type, and the gut microbiome [3, 6].

Over the past few years, several studies have explored the correlation between changes in the gut microbiome and intestinal or extra-intestinal immune-mediated disorders, such as inflammatory bowel disease, irritable bowel syndrome, obesity, rheumatoid arthritis, ankylosing spondylitis, multiple sclerosis, autoimmune uveitis, types 1 and 2 diabetes, and AMD [1-3, 7].

Zinkernagel et al. [8] found an abundance of *Anaerotruncus* spp., *Oscillibacter* spp., *Eubacterium ventriosum*, and *Ruminococcus torques* in patients with neovascular AMD than in control groups who exhibited an abundance of *Bacteroides eggerthii* instead, which has a protective role against immune-mediated diseases. Lin et al. [9] found an increased number of *Prevotella spp.* and a reduced number of *Rikenellaceae* populations. Therefore, it of interest to further investigate the gut microbiome and its role in pathogenesis of AMD, which could lead to new treatment strategies.

Table 1. Characteristics of Included Articles Related to the Role of Intestinal Microbiome in the Pathogenesis of Age-Related Macular Degeneration

No.	Study	Title	Journal	Date of publish	Type of study
1	Lin [1]	Importance of the intestinal microbiota in ocular inflammatory diseases: A review.	Clin Exp Ophthalmol.	2019	Review
2	Baim et al. [2]	The microbiome and ophthalmic disease.	Exp Biol Med (Maywood)	2019	Review
3	Lin [3]	The role of the intestinal microbiome in ocular inflammatory disease.	Curr Opin Ophthalmol.	2018	Review
4	Belkaid et al. [4]	Role of the microbiota in immunity and inflammation.	Cell	2014	Review
5	Chervonsky [5]	Microbiota and Autoimmunity	Cold Spring Harb Perspect Biol.	2013	Review
6	Zheng et al. [6]	Interaction between microbiota and immunity in health and disease.	Cell Res.	2020	Review
7	Forbes et al. [7]	The Gut Microbiota in Immune-Mediated Inflammatory Diseases	Front Microbiol.	2016	Review
8	Zinkernagel et al. [8]	Association of the Intestinal Microbiome with the Development of Neovascular Age-Related Macular Degeneration.	Sci Rep.	2017	Metagenome analysis
9	Lin et al. [9]	HLA-B27 and human β2-microglobulin affect the gut microbiota of transgenic rats.	PLoS One.	2014	Experimental study
10	Nayyar et al. [10]	Do epigenetic changes caused by commensal microbiota contribute to development of ocular disease? A review of evidence.	Hum Genomics.	2020	Review
11	Andriessen et al. [11]	Gut microbiota influences pathological angiogenesis in obesity-driven choroidal neovascularization.	EMBO Mol Med.	2016	Experimental study
12	Rowan et al [12]	Gut microbiota modify risk for dietary glycemia-induced age-related macular degeneration.	Gut Microbes	2018	Experimental study (metabolomics study)
13	Carneiro et al. [13]	Nutritional and Lifestyle Interventions for Age-Related Macular Degeneration: A Review	Oxid Med Cell Longev.	2017	Review
14	Margrain et al. [14]	Do blue light filters confer protection against age-related macular degeneration?	Prog Retin Eye Res.	2004	Review
15	de Jong [15]	Age-related macular degeneration.	N Engl J Med.	2006	Review
16	Zhang et al. [16]	Overweight, Obesity, and Risk of Age-Related Macular Degeneration.	Invest Ophthalmol Vis Sci.	2016	Review
17	Peeters et al. [17]	Changes in abdominal obesity and age-related macular degeneration: the Atherosclerosis Risk in Communities Study.	Arch Ophthalmol.	2008	Population-based cohort study
18	Chiu et al. [18]	Dietary hyperglycemia, glycemic index and metabolic retinal diseases.	Prog Retin Eye Res.	2011	Review
19	Rinninella et al [19]	The Role of Diet, Micronutrients and the Gut Microbiota in Age-Related Macular Degeneration: New Perspectives from the Gut–Retina Axis.	Nutrients	2018	Review
20	Lau et al. [20]	Bridging the Gap between Gut Microbial Dysbiosis and Cardiovascular Diseases.	Nutrients	2017	Review
21	Ma et al. [21]	Gut Microbiota and Nonalcoholic Fatty Liver Disease: Insights on Mechanisms and Therapy.	Nutrients	2017	Review
22	Ponziani et al. [22]	Hepatocellular Carcinoma Is Associated With Gut Microbiota Profile and Inflammation in Nonalcoholic Fatty Liver Disease.	Hepatology	2019	Prospective study
23	Turnbaugh et al. [23]	An obesity-associated gut microbiome with increased capacity for energy harvest.	Nature	2006	Comparative study
24	Adams et al. [24]	Abdominal obesity and age-related macular degeneration.	Am J Epidemiol.	2011	Prospective cohort study
25	Clarke et al. [25]	The gut microbiota and its relationship to diet and obesity: new insights.	Gut Microbes.	2012	Review
26	Rabot et al. [26]	Germ-free C57BL/6J mice are resistant to high-fat-diet-induced insulin resistance and have altered cholesterol metabolism.	FASEB J.	2010	Experimental study
27	Ticinesi et al. [27]	Aging Gut Microbiota at the Cross-Road between Nutrition, Physical Frailty, and Sarcopenia: Is There a Gut-Muscle Axis?	Nutrients	2017	Review
28	Evans et al. [28]	Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration.	Cochrane Database Syst Rev.	2017	Systematic Review
29	Abd et al. [29]	Aged macular degeneration: current therapeutics for management and promising new drug candidates.	Drug Discov Today	2017	Review
30	Ahmadi et al. [30]	Epigenetic modifications and epigenetic based medication implementations of autoimmune diseases.	Biomed Pharmacother.	2017	Review
31	Ramadoss et al. [31]	Targeting the cancer epigenome: synergistic therapy with bromodomain inhibitors.	Drug Discov Today	2018	Review
32	Cheung et al. [32]	BET N-terminal bromodomain inhibition selectively blocks Th17 cell differentiation and ameliorates colitis in mice.	Proc Natl Acad Sci	2017	Experimental study
33	Eskandarpour et al. [33]	Pharmacological Inhibition of Bromodomain Proteins Suppresses Retinal Inflammatory Disease and Downregulates Retinal Th17 Cells.	J Immunol.	2017	Experimental study
34	Hammitzsch et al. [34]	CBP30, a selective CBP/p300 bromodomain inhibitor, suppresses human Th17 responses.	Proc Natl Acad Sci U S A.	2015	Experimental study
35	Wen et al. [35]	Epigenetics, microbiota, and intraocular inflammation: New paradigms of immune regulation in the eye.	Prog Retin Eye Res.	2018	Review
36	Markowiak et al. [36]	Effects of Probiotics, Prebiotics, and Synbiotics on Human Health.	Nutrients	2017	Review
37	Gilbert et al. [37]	Microbiome-wide association studies link dynamic microbial consortia to disease.	Nature	2016	Review
38	Zegans et al. [38]	Considerations in understanding the ocular surface microbiome.	Am J Ophthalmol.	2014	Editorial
39	Dong et al. [39]	Diversity of bacteria at healthy human conjunctiva.	Invest Ophthalmol Vis Sci.	2011	DNA sequencing-based study
40	Lu et al. [40]	Human Microbiota and Ophthalmic Disease.	Yale J Biol Med.	2016	Review
41	Knight et al. [41]	The Microbiome and Human Biology.	Annu Rev Genomics Hum Genet.	2017	Review

The Gut-Eye Axis: Intestinal Microbiome in AMD

AMD is one of the most common causes of blindness in the elderly population. Although its pathogenesis is unclear, genetic and environmental factors, such as a Western diet (a high-caloric, high-fat, and simple sugar-based diet), a diet low in omega-3 fatty acids, smoking, as well as genetic variants of complement and genes related to other inflammatory or lipid pathways are thought to be involved. Some inflammatory mechanisms linked to innate immunity such as NLR family pyrin domain containing 3 (NLRP3) receptors, complement pathways, and tool-like receptors may play a role in the progression of AMD. These pathways are strongly linked to human commensal intestinal microbiota [1].

In the largest genome-wide study on AMD patients, genetic variants were observed to be associated with the disease at 34 loci. These data are only a part of the genomic heritability of AMD. Of these variants, the ones most strongly linked to AMD were the complement pathway gene variants, such as the complement factor H (CFH) and complement factor I (CFI) genes (both regulators of the complement cascade), as well as age-related maculopathy susceptibility 2 (ARMS2) gene. Other gene variants, for example, lipid-associated pathway genes such as apolipoprotein E (Apo E), and the hepatic lipase (LIPC), which represent the lipid metabolism pathway and tissue inhibitor of metalloproteinase 3 (TIMP3), were associated with AMD. All patients with AMD also have drusen, which contains complement lipoproteins and lipids. They also usually present with overactivity of the complement. Studies have shown that alterations in intestinal microbiome are thought to be an environmental causative agent for elevated levels of complement through the complement c ascade [1].

Besides, genetic risk factors of AMD, environmental factors such as diet, smoking, and hypertension also play an important role in the progression of AMD. Accordingly, suggestions provided by the Age-Related Eye Disease Study (AREDS) and AREDS2 on diet modifications have slowed down the progression of dry AMD to wet AMD in some patients. Intestinal microbiota also appear to have an impact on the dietary intake of nutrients [10].

Intestinal microbiome dysbiosis often occurs along with chronic inflammation and enhanced intestinal permeability. This is followed by elevated levels of pathogen-associated molecular pattern molecules (PAMPs) and bacterial by-products in the circulation, triggering an immune response through their interaction with pattern recognition receptors (PRRs). PRRs are also expressed in ocular cells, leading to ocular inflammation. These data signify a connection between AMD and dysbiosis of the gut microbiome [10].

Animal studies, such as that of Andriessen et al., have shown an association between alterations in gut microbiome, choroidal neovascularization (CNV), and diet in mice. They evaluated this hypothesis by transplanting gut microbiota from mice fed a regular diet into mice fed a high-fat diet. A high-fat diet appeared to increase the progression of CNV; however, the progression decreased when the Bacteroidetes/Firmicutes ratio in intestinal microbiome increased in the regular diet-fed mice. A study revealed that oral administration of an antibiotic, neomycin, changed the bacterial flora in mice fed a high-fat diet, leading to a delayed progression of CNV [11]. In another animal study by Rowan et al., mice administered a high-glycemic index diet showed increased levels of dry AMD features compared to those fed a low-glycemic index diet. The authors also described some alterations in intestinal microbiota between the two groups. Serotonin, a tryptophan metabolite, which is thought to have an inhibitory effect on AMD features, was elevated in mice fed a low-glycemic index diet. These findings support the concept of a gut-retina axis, in which alterations in intestinal microbiota via diet, probiotics, or antibiotics influence the onset and progression of AMD [12].

Dietary Factors and Gut-Microbiota in AMD

Although pathogenetic mechanisms of AMD have not yet been clearly defined, there are studies showing that inflammation may play a role in its pathogenesis. The retinal pigment epithelium (RPE) is exposed to high oxygenation levels. High levels of unsaturated fatty acids and photosensitizing compounds have been shown to cause retinal damage via adverse effects of reactive oxygen species (ROS) [13]. Light exposure, including ambient natural light, induces the formation of ROS in the RPE and is considered to be one of the less recognizable but common risk factors of AMD [14]. Smoking, given its pro-oxidative and pro-inflammatory effects, is a more recognizable modifiable risk factor of AMD [15]. Pathogenesis and progression of AMD have been associated with a wide range of factors, including age, environmental factors, genetics, lifestyle, and diet. Excess weight has been linked to a higher risk of AMD and shows a dose-dependent trend [16, 17], and excess sugar consumption related to modern dietary habits has also been correlated with AMD [18]. Contribution of various nutritional and non-nutritional compounds (that exceed the essential energy intake) in AMD has been demonstrated in several epidemiological studies [19] .

Nutrients may have a direct antioxidant or anti-inflammatory effect, or act indirectly through the gut

microbiome [19]. This has led to an interest in the efficacy of nutraceuticals and functional foods rich in prebiotics and antioxidants in the prevention and supplementation of anti-AMD pharmacological treatments [19].

Over the last decade, intestinal dysbiosis has been associated with a wide spectrum of intestinal and extra-intestinal pathologies, including inflammatory and metabolic diseases, non-alcoholic fatty liver disease (NAFLD), obesity, and cancer [20-24]. Increased gut permeability allows excessive translocation of bacterial products, such as PAMPs and endotoxin lipopolysaccharides, which leads to low-grade inflammation in various tissues via the activation of PRRs. Interestingly, this biological crosstalk is also observed in perivascular macrophages, dendritic cells, and RPE cells, contributing to the ocular inflammatory process. Additionally, retina-specific immune cells have been observed to be regulated by metabolites of intestinal microbiota, whereas obesity-related gut microbiota has been found to cause pathological angiogenesis and eventually CNV in retinal tissue [11].

Evidence from experimental studies has shown that ob/ob mice (mutant mice that consume excessive amounts of food because of mutations in the leptin gene) exhibit a 50% decrease in Bacteroidetes and an increase in Firmicutes compared to lean mice [24]. Administering a Western diet to wild-type mice reduced the diversity of intestinal microbiota, especially of Bacteroidetes, and displayed an increase in a single class of Firmicutes (Mollicutes) [25]. This "obesity-associated gut microbiome" has been demonstrated to have an increased propensity to recruit energy from diet by breaking down otherwise indigestible dietary polysaccharides [23]. Interestingly, this increased adiposity revealed to be a transmissible feature: adult germ-free mice colonized (by gavage) with microbiota of obese (ob/ob) donors demonstrated a substantially higher increase in body fat over a two-week period compared to mice colonized with microbiota from lean donors fed with food having the same quantity and caloric density [23]. Furthermore, a high-fat diet does not lead to hypercholesterolemia or weight gain in the absence of gut microbiota, as exhibited in germ-free C57BL/6J mice compared to wild-type mice. Another trait of germ-free mice is that they show improved insulin sensitivity and improved glucose tolerance compared to conventional mice [26]. These findings validate the fact that gut microbiota plays a critical role in metabolic pathways of low-grade inflammation and obesity. After the age of 65 years, intestinal microbiota in humans has been shown to undergo important alterations that affect its resilience to antibiotics or diseases. This is especially true in frail patients [27]. Besides, gut microbiota is a critical parameter that plays a role in the absorption and metabolism of macro- and micronutrients, especially microbiota related to AMD [27]. The use of vitamins and other anti-oxidative micronutrients can reduce the risk of AMD due to their anti-inflammatory and antioxidant properties [28]. However, the impact of high-fat, high-glucose, or fructose diets, as well as the role of substances such as micronutrients, vitamins (C, D, and E), carotenoids, lutein, zeaxanthin, and omega-3 fatty acids need further research to prove their effects.

The current published evidence has shown that the concept of "gut-retina axis" exists in the pathogenesis of AMD [1-3]. It appears that an interplay among diet, micronutrients, gut microbiota, and host immunity is a new frontier in the treatment of several other metabolic disorders. However, the exact effect of these dietary parameters on gut microbiota and the pathogenesis of AMD is beyond the scope of this review.

Therapeutic Targeting of Intestinal Microbiome for Ocular Inflammatory Disease

The activity of microorganisms present in the eye can trigger intraocular inflammation. The triggering of immune responses is linked with alterations of epigenomes in cells associated with innate and adaptive immunity, leading to the production of immune mediators (such as cytokines), recruitment of immune cells to the site of inflammation, and finally destruction and/or recovery of the tissues. Therefore, various therapeutic approaches have been developed to suppress intraocular inflammatory activity. In AMD, intravitreal anti-vascular endothelial growth factor (VEGF) agents are used to prevent the progression of CNV and eventually vision impairment in patients with wet AMD. However, effective therapeutic modalities for dry AMD are yet to be discovered [29].

Recent advances in the field of epigenetic drugs that target epigenetic machinery, including writers, readers, and erasers of epigenetic modifications, may lead to new tools for immunosuppressive treatment [30]. Among these drugs, histone methyltransferase inhibitors (HMTis), histone deacetylase inhibitors (HDACis), DNA methyltransferase inhibitors (DNMTis), and bromodomain extra-terminal (BET) inhibitors have been approved for the treatment of other clinical diseases, such as malignancies [31]. In addition, various compounds, such as JQ1 (a bromodomain inhibitor) [32-34], have shown promising immunosuppressive effects in the real world. The success of these drugs relies on their potential effect on controlling intraocular inflammation after local or systemic administration. Specificity of these epigenetic drugs is derived from their ability to target the cell types of specific epigenetic regulatory networks. Furthermore, they can control multiple cytokines and immune mediators rather than a single cytokine, which further enhances their effectiveness in controlling intraocular inflammation [35].

Although the pathogenetic background of AMD related to infection has garnered much attention, targeting microbiota for designing new treatments still remains debatable. Attempts to restore intraocular and extraocular imbalance of microbiota may lead to further problems due to the development of resistance to antibiotics, especially when they are used to eliminate pathogenic bacteria, resulting in other ocular diseases. Recent studies have suggested that combined therapies with probiotics and prebiotics have a great potential to treat dysbiosis of gut microbiota [36].

The present review, albeit its strengths, has several limitations. This study is a review of literature on the correlation between AMD and gut microbiota. As summarized in Table 1, this review covers a wide spectrum of aspects regarding this issue without duplication of data. Most of the references included in this review comprised studies published within the last five years. In addition, special emphasis was placed on reports that provided the most updated information. However, in the present literature review, there is a possibility that all relevant literature has not been included, thus increasing the probability of bias in concluding the data. Additionally, the number of human studies is limited, and most of our knowledge regarding the impact of microbiome on AMD is based on experimental data.

Future perspectives on the microbiome of human body will be worth noting, and recognizing its importance will improve our understanding of the pathogenesis of several immune-mediated human diseases. Refinement of laboratory and experimental techniques has also enabled researchers to define compositional and functional aspects of these microbiotas. New assays and bioinformatic studies have allowed a more detailed analysis of host-microbiota interactions, whereas large-scale longitudinal studies have provided new insights regarding the effect of microbiotas on various pathogenetic mechanisms. Nevertheless, clinical trials are essential for investigating microbiotas as potential biomarkers and uncovering their potential role in the prevention or treatment of immune-mediated diseases [2, 37]. The microbiome related to ophthalmology has opened up a new field of research; however, it is yet to be determined how it can be used in treating ophthalmic diseases in humans [38-40]. Implementation of methods gained from other fields of microbiome research would be invaluable in exploring the pathogenesis of ophthalmological diseases. Gaining insights into host biology can contribute to understanding whether microorganisms are temporarily present and are rapidly inactivated or whether they are persistently present, leading to more permanent and active communities. Gnotobiotic animal models used in microbiome research may also be helpful in conducting ophthalmological research in this field [37]. However, novel experimental techniques and larger clinical trials have established a more solid connection between basic science and observational research in this field.

Further experimental investigations may uncover an association between extraocular microbiome and ocular diseases, or even ophthalmic interventions (e.g., intravitreal injections of anti-VEGF and topical instillation of cyclosporine), which may potentially affect ocular microbiota).

CONCLUSIONS

Increasing evidence has revealed that an imbalance between beneficial and harmful microbes of intestinal microbiota or intestinal dysbiosis may play an important role in the pathogenesis of AMD. Defining the exact role of intestinal microbiome will help us understand pathogenetic mechanisms and indicate potential treatment options for AMD. Targeting gut microbiota via dietary alterations, probiotics, bacterial metabolite supplementation, fecal microbial transplantation, or antibiotics could be a potential option for preventing the progression of AMD. With time and larger longitudinal animal and clinical studies, future advances in microbiome research will be promising and may unveil a new era in the treatment of AMD.

ETHICAL DECLARATIONS

Ethical approval: This study is a review and no ethical approval was required.
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