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The role of microbiome in uveitis

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Abstract

The gut microbiota comprises a complex bacterial community that resides in the intestine. Imbalances in the gut microbiota can disrupt immune homeostasis, triggering autoimmune diseases including non-infectious uveitis. Despite recent advances, the underlying mechanisms linking the microbiome and uveitis are not fully understood. This review offers a comprehensive analysis of the literature addressing microbiome's relationship with ocular inflammation. Additionally, it explores the potential of modulating the gut microbiota as a novel therapeutic target. A literature search of published articles related to the role of ocular microbiome in non-infectious uveitis in PubMed and Scopus databases was conducted. The following keywords were used: microbiome, uveitis, and immune-mediate diseases.

Keywords

Microbiome, uveitis, autoimmune

Introduction

While uveitis is a diverse and complex disease, the prevailing belief is that a combination of environmental and genetic factors, coupled with immune-mediated inflammation, plays a crucial role in its onset and progression. The condition is caused by a disturbed balance between the regulatory and effector components of the immune system, a phenomenon marked by a complex interplay of pro- and anti-inflammatory factors leading to the destruction of the immune-privileged tissues, specifically those of the eye [1].

The process of colonization by bacteria following birth plays a fundamental role in shaping the human immune system whereby the body's surfaces become covered by innumerable bacteria by the time of adulthood. The term "microbiome" is used to refer to these wide varieties of microorganisms [2].

The etiology of uveitis is diverse; it could be infectious, immune-mediated, iatrogenic, or undetermined etiologies. This literature review compiles existing research on the correlation between microbiota and

non-infectious uveitis (NIU). There are contradictory findings suggesting that the relationship between microbiota and uveitis may be more complex than initially thought. While further research is needed to fully understand this relationship, the existing literature highlights the various mechanisms through which intestinal dysbiosis may contribute to the pathogenesis of NIU as well as the potential value of microbiome-based interventions for the prevention and treatment of uveitis.

Methodology

A search of published articles related to the role of microbiome in uveitis was conducted. The literature review of published articles was done using PubMed and Scopus databases. The following search terms in various combinations were used: non-infectious uveitis, gut microbiome, dysbiosis, and HLA.

Gut microbiome

The microbiome is a complex ecosystem that varies in population and diversity according to different factors such as age, genetics, diet, lifestyle, and environmental factors [2]. Studies have shown that disruptions in the balance of the microbiome, known as dysbiosis, can result in immune dysregulation, thereby contributing to the development of various autoimmune disorders such as inflammatory bowel disease (IBD) [3]. Furthermore, the research has established a link between the intestinal microbiota and extraintestinal disorders like multiple sclerosis (MS), fibromyalgia, arthritis, and mental disorders. However, some experts argue that the current body of evidence is insufficient to definitively establish a causal relationship between gut health and extraintestinal diseases [2]. However, studies on mice have shown that changes in the composition of gut microbiota can modulate cytokine production and T-cell activation, which can influence the development of autoimmune diseases in the eyes [4].

The human gut microbiome comprises approximately 160 bacterial species, the majority can be classified into three groups based on their physiological functions: fermentative bacteria, bile-tolerant bacteria, and mucin-degrading bacteria [5, 6]. The fermentative bacteria produce a range of organic acids as end products of carbohydrate fermentation. These include short-chain fatty acids (SCFAs) such as butyrate, succinate, and propionate, which play a vital role in the physiology of the gastrointestinal tract and the overall health of the host [7].

The group of butyrate-producing bacteria (BPB) is considered a significant anti-inflammatory bacterial population [8]. This group, consisting of bacterial species like *Faecalibacterium*, *Blautia*, *Roseburia*, *Lachnospira*, and *Ruminococcus*, has potential benefits such as modulation of immune response and production of butyrate, which stimulates the production of immunosuppressive regulatory T (Treg) cells as well as inhibits the expression of proinflammatory mediators. Additionally, it encourages mucin secretion, which strengthens and protects the gastrointestinal epithelial barrier [9–12].

A reduction in butyrate production may result in a disruption of the gut microflora equilibrium, thereby causing a decline in the Treg cells and the initiation of T-effector responses. These changes may have long-term consequences for both the composition of the gut microbiota and the efficiency of the immune system [12]. Methanogens, including the *Candidatus*, *Methanomethylophilus*, and *Methanoculleus* bacterial species, constitute an additional category of beneficial bacteria which produce methane that has anti-inflammatory and anti-apoptotic effects on intestinal as well as retinal tissues [12].

Pathogenic microbes with proinflammatory properties include sulfate-reducing bacteria (SRB) like *Bilophila* spp. and opportunistic pathogens like *Parabacteroides* spp., *Paraprevotella* spp., and *Fusobacterium* spp. Hydrogen sulfide (H_2S), produced during sulphate reduction by SRB, inhibits butyrate metabolism in intestinal cells. Additionally, this gas promotes inflammatory response in the gut by disrupting the integrity of the intestinal barrier and thereby exposing the intestinal epithelium to bacterial products [13, 14]. These SRB have been detected in the microbiota of patients with autoimmune uveitis. Additionally, several studies have compared the bacterial profiles of individuals with uveitis to those of healthy individuals. The results revealed a shift in the microbial community structure which may suggest a disruption in the balance between protective (symbiotic) and harmful (pathogenic) microorganisms.

Particularly, uveitis patients exhibited a significant reduction in protective microorganisms, coupled with an increase in gut proinflammatory bacteria. While protective (symbiotic) bacteria with anti-inflammatory effects are more common in healthy individuals [12, 15].

The mechanism by which this disruption can contribute to the development of NIU is an area of interest to many researchers. The following section will illustrate the various mechanisms suggested in the literature.

The mechanism underlying dysbiosis-induced uveitis

In recent years, there has been a growing interest in studying the role of microbiota in the development of NIU [16]. Dysbiosis is involved in the development of uveitis through four complementary mechanisms, which include antigenic or molecular mimicry, increased intestinal permeability, loss of immune intestinal homeostasis, and reduced production of beneficial anti-inflammatory metabolites [17].

Molecular mimicry

Antigenic mimicry is a prominent mechanism that contributes to the development of autoimmune diseases. In this process, the production of autoreactive T cells is a direct consequence of the cross-reactivity that exists between self-antigens and microbial peptides. As a result, pro-inflammatory cytokines are produced, causing tissue damage and inflammation [18].

Studies conducted on mice with experimental autoimmune uveitis (EAU) have demonstrated the role of this pathogenic mechanism since the severity of uveitis can be reduced and intestinal T helper 17 cells (Th17, effector T cells) activation can be minimized by administering oral broad-spectrum antibiotics, which eliminate the microbial community. In contrast, the transfer of T cells from a microbiota-grown transgenic mouse can induce uveitis in wild mice [4].

Loss of intestinal immune homeostasis

Dysbiosis results in the disruption of intestinal homeostasis, leading to an imbalance between effector T cells (Th1 and Th17) and Treg cells, which in turn triggers immune activation by upregulating Th17 [and interleukin 17 (IL-17)] and downregulating Treg (and IL-10) [19, 20]. For example, *Klebsiella* triggers the activation of Th (Th1) cells in the intestinal region through antigen-presenting cells (APCs), resulting in the secretion of inflammatory mediators like tumor necrosis factor alpha (TNFα) and interferon gamma (IFNγ). *Bacteroides fragilis* is known to generate polysaccharide A, which stimulates Treg cells. *Bifidobacterium* has been observed to stimulate Treg cells as well, which are known to mitigate inflammation by regulating the activity of Th1, Th2, and Th17 cells [21]. In addition, it has been observed that mice models with EAU showed the presence of T cells originating from the intestine within their ocular tissues, thereby providing evidence in favor of the migration of immune cells from the gut to the eye (gut-eye axis) [1, 22].

Increased intestinal permeability

Although the intestinal barrier is naturally permeable to some degree, an increase in permeability resulting from dysbiosis-induced mucosal inflammation, facilitates the translocation of microbiota or its products to the circulation [23, 24]. These products, namely lipopolysaccharides (LPS) and β-glucan can disseminate throughout various tissues via the vascular system. This can result in the direct induction of inflammation within targeted organs such as the uveal tissue. The study conducted by Janowitz et al. [25] focused on examining intestinal alterations in mice with EAU induced by immunization with inter-photoreceptor retinoid-binding protein (IRBP) along with killed *Mycobacterium tuberculosis* (MTB) antigen as an adjuvant. The control group consisted of mice that were immunized with MTB, which did not exhibit any ocular inflammation. The research findings indicate that there was a noticeable increase in intestinal permeability in mice that were immunized with IRBP, as compared to those that were not immunized. This increase in permeability was found to be consistent with the progression of uveitis along with alterations in the composition of the intestinal microbiota [25].

Reduction of anti-inflammatory microbial metabolites

Numerous metabolites produced by gut microbiota have the potential to modulate immune responses. SCFAs have been previously mentioned, and are produced via the process of dietary fiber fermentation which offers anti-inflammatory effects by stimulating and enhancing Treg cells in the intestinal lamina propria, while also inhibiting effector T cells and reducing their migration between the intestine and spleen [22, 26]. It was found that adding SCFAs to the diet from outside sources reduced the severity of uveitis in mice with EAU [22, 27].

From an immunological perspective, it is necessary to present retinal antigens to the immune system to develop autoimmune uveitis. The following section will delve into the hypothesis of the gut-eye axis.

The gut-eye axis

The ocular and brain tissues have been recognized as areas of immunological privilege. The sequestration of target antigens behind the blood-retinal barrier and blood-brain barrier leads to their inaccessibility to the immune system, thereby impeding the activation of self-reactive T cells that have bypassed thymic negative selection and are present in the bloodstream [28, 29]. There is a strong correlation between IBD and ocular inflammatory conditions, as approximately 10% of patients with IBD can develop episcleritis, uveitis, and conjunctivitis [4]. Multiple studies have demonstrated the presence of a gut-eye axis, wherein gut microbiota can impact the immune response in the eye. Furthermore, as previously stated, numerous studies have highlighted the significance of the intestinal microbiome and its metabolites, specifically SCFAs, in the modulation of essential immune cell functions [30, 31]. NIU is an example of many ocular conditions that have been linked to abnormalities in the gut microbiome; others include glaucoma, diabetic retinopathy, and age-related macular degeneration [30, 31].

The study conducted by Nakamura et al. [1] showed a significant reduction in uveitis severity in the EAU model following oral administration of specific antibiotics. However, when the antibiotics were administered intraperitoneally, no effect was observed. These findings underscore the crucial role of gut microbiota in influencing uveitis in this model. Moreover, the improvement of uveitis seems to be linked with significant changes in bacterial species caused by the administration of oral antibiotics. This leads to the differential buildup of effector (Th1 and Th17) and Treg-cell populations in different lymphoid tissues, including the intestinal lamina propria and cervical lymph nodes located near the eye. Additionally, Horai et al. [28] demonstrated in their research that the microbiota present in the gastrointestinal contents of immunized mice exhibited modifications in comparison to non-immunized mice. As well, antibiotic-treated mice in the EAU study revealed a diverse microbial composition, which conferred a protective effect against uveitis [32].

However, in contrast to the experimental disease, most cases of human autoimmune uveitis cannot be attributed directly to an immune system exposure to ocular antigens since these antigens are typically sequestered behind a tight blood-retinal barrier in a healthy eye. This presents a paradoxical situation as retinal antigens are not typically expressed in the periphery and the activation of retina-specific T cells circulating in the periphery is a crucial step to be able to breach the blood-retinal barrier and trigger inflammation. This scenario prompts fundamental research regarding the location and manner in which autoreactive T cells, capable of recognizing retinal antigens and initiating uveitis, are initially stimulated [28].

To study this scenario, the spontaneous uveitis model in R161H mice was used to elaborate the role of microbiota in activating the retina-specific T cells and triggering autoimmune uveitis. The administration of oral broad-spectrum antibiotics to R161H mice prior to birth led to a depletion of commensal microbiota. This resulted in a significant reduction of spontaneous uveitis, which was also observed in R161H mice raised under germ-free conditions. The development of uveitis was found to be correlated with an elevated population of Th17 cells in the intestinal lamina propria. In mice that were either treated with antibiotics or were germ-free, these Th17 cells were observed to be significantly diminished. These findings provide

robust evidence in support of the hypothesis that commensal microbiota plays a significant role in the pathogenesis of spontaneous uveitis [4].

Clinical studies

Preclinical studies conducted on EAU models have demonstrated the involvement of the gut microbiome in the pathogenesis of various immune or inflammatory diseases, such as Behcet's disease (BD) [33], Vogt-Koyanagi-Harada disease (VKH), rheumatoid arthritis (RA) [34], psoriatic arthritis (PsA), IBD [35], MS [36], spondylarthritis (SpA) [37], and systemic lupus erythematosus (SLE), as shown in Table 1 [38, 39]. While clinical studies are necessary to characterize dysbiosis of the gut microbiome and its role in modulating immune homeostasis, it is challenging to draw causal conclusions from these studies.

Table 1. Characterization of gut dysbiosis in different autoimmune conditions compared to healthy or disease controls

Disease	Author	Study object	Study findings	
			Increased microbiota	Decreased microbiota
BD	Yasar et al., 2020 [40]	27 BD *vs.* 10 HCs	*Lachnospiraceae* NK4A136, *Actinomyces*, *Libanicoccus*, *Collinsella*, *Eggerthella*, *Enetrohabdus*, *Catenibacterium*, *Enterobacter*	*Bacteroides*, *Cricetibacter*, *Alistipes*, *Lachnospira*, *Dielma*, *Akkermansia*, *Sutterella*, *Anaerofilum*, *Ruminococcease-UCG007*, *Acetanaerobacterium*, *Copropaacter*
	Shimizu et al., 2019 [41]	13 BD *vs.* 27 HCs	*Eggerthella lenta*, *Acidaminococcus bifidum*, *Lactobacillus iners*, *Streptococcus* species, *Lactobacillus salivarius*	*Megamonas hypermegale*, *Butyrivibrio*, *Streptococcus infantis*, *Filifacto*
	Oezguen et al., 2019 [42]	13 BD *vs.* 14 HCs	*Parabacteroides*, *Clostridiales*, *Geminger*, *Butyricimonas*, *Actinobacteria*, Erysipelotrichaceae	*Vampirovibrio*, unclassified Lachnospiraceae, *Prevotella*
	Ye et al., 2018 [33]	32 BD *vs.* 74 HCs	*Bilophila* spp., *Parabacteroides* spp., *Paraprevotella* spp., *Stenotrophomonas* spp., *Actinomyces* spp., *Corynebacterium* spp.	*Clostridium* spp. (BPB), *Methanoculleus* spp., *Methanomethylophilus* spp.
VKH	Ye et al., 2020 [39]	55 VKH *vs.* 52 HCs	*Ramularia*, *Alternaria*, *Rhizophagus*	*Methanoculleus*, *Candidatus Methanomethylophilus*, *Azospirillum*
	Li et al., 2022 [43]	11 VKH *vs.* 11 HCs *vs.* 20 NIAS	*Stomatobaculum*, *Pseudomonas*, *Lachnoanaerobaculum*	*Gordonibacter*, *Slackia*
AS	Zhang et al., 2020 [44]	20 AS *vs.* 19 HCs	Prevotellaceae, Actinomycetaceae, *Dialister*, *Escherichia-Shigella*, *Klebsiella*	Lachnospiraceae, *Bacteroides*, *Parasutterella*, *Bifidobacterium*
	Yin et al., 2020 [45]	127 AS *vs.* 123 HCs	*Clostridiales* bacterium 1_7_47FAA, *Clostridium hatheway*, *Clostridium bolteae*	*Bifidobacterium adolescentis*, *Coprococcus comes*, *Lachnospiraceae* bacterium 5_1_63FAA, *Roseburia inulinivorans*
	Klingberg et al., 2019 [46]	150 AS *vs.* 17 HCs	Proteobacteria, Enterobacteriaceae, Bacilli, *Streptococcus* species, Actinobacteria	*Bacteroides*, Lachnospiraceae
IBD	Takahashi et al., 2016 [47]	10 IBD *vs.* 10 HCs	*Actinomyces*, *Bifidobacterium*	*Bacteroides*, *Eubacterium*, *Faecalibacterium*, *Ruminococcus*
	Franzosa et al., 2019 [48]	121 IBD *vs.* 34 HCs	*Bifidobacterium breve*, *Clostridium symbiosum*, *Ruminococcus gnavusa*, *Escherichia coli*, *Clostridium clostridioforme*	*Roseburia hominis*, *Dorea formicigenerans*, *Ruminococcus obeum*

HCs: healthy controls; AS: ankylosing spondylitis; NIAS: non-infectious anterior scleritis

Numerous investigations conducted on particular disease populations, including BD and VKH disease, have established a robust correlation primarily by comparing the microbiome of patients with the disease to that of healthy individuals [33, 39].

Clinical investigations conducted on patients with BD have revealed a modification in the microbiota composition, along with notable variations in the gut microbiome composition between BD patients with and without uveitis [33]. This implies a correlation between intestinal dysbiosis and the pathophysiology of the disease. The observed alterations primarily consisted of a rise in SRB, *Stenotrophomonas* species, *Actinomyces* species, and *Paraprevotella* species, accompanied by a decline in BPB and methanogens. The lack of equilibrium leads to impairment of the intestinal epithelial barrier, thereby promoting the

infiltration of effector molecules into the intestinal epithelial cells [49–51]. A study conducted by Emmi et al. [52] wherein patients with BD were randomly assigned to receive diets enriched with butyrate. The findings of the study indicate a decrease in disease activity and a reduction in the use of immunosuppressive medication, despite the lack of significant changes in blood inflammatory markers [52].

The microbial composition of the intestinal microbiome in patients diagnosed with active VKH disease exhibits differences in comparison to that of healthy individuals, which is akin to the observed differences in patients with BD. Specifically, *Paraprevotella* spp. were enriched in active VKH patients, whereas BPB like *Clostridium* spp. and methanogens like *Methanoculleus* spp. were depleted [39, 43].

Regarding the SpA disease spectrum, the initial evidence linking SpA and intestinal inflammation was derived from histological analysis of tissue obtained during colonoscopy as part of a research study involving patients with SpA and no apparent intestinal symptoms. The study revealed that over 50% of patients exhibited subclinical or unrecognized inflammation associated with heightened levels of intestinal permeability. Moreover, reactive arthritis and acute anterior uveitis (AAU) can also be triggered by a range of enteric infections such as *Salmonella*, *Yersinia*, *Shigella*, and *Campylobacter*. Furthermore, the efficacy of sulfasalazine in addressing arthritis associated with SpA may be ascribed to its established influence on the intestinal microbiota and its ability to reduce intestinal permeability [23].

A comparative analysis was conducted to examine the composition of gut microbiota in patients with SpA in relation to healthy controls. The results revealed a higher level of microbial richness in SpA patients. Furthermore, an observed positive correlation has been identified between the abundance of the bacterial genus *Dialister* and the level of inflammatory activity in SpA. This suggests that *Dialister* has the potential to serve as an indicator of disease activity [53].

The role of human leukocyte antigen

The human leukocyte antigen (HLA), also known as the major histocompatibility complex (MHC) is responsible for antigen presentation. However, the precise mechanism through which HLA molecules confer susceptibility to diseases is frequently not understood. HLA molecules have been observed to exert an impact on the susceptibility of certain immune-mediated diseases, including ankylosing spondylitis [54], birdshot chorioretinopathy (BSRC) [55], and Crohn's disease [56], wherein the presence of autoantibodies is not an essential aspect of the condition. This implies that in the aforementioned illnesses, the susceptibility produced by the HLA allele may not be working through an autoimmune reaction. Given that the gut microbiome plays a role in educating the immune response and exhibits a wide range of antigenic diversity, it is plausible to consider an alternative hypothesis that HLA molecules may, in certain cases, contribute to disease susceptibility through their impact on the gut microbiome [23]. To test this hypothesis that HLA molecules would influence the intestinal bacterial composition, the microbiome of HLA-B27-transgenic mice that express HLA-B27, was compared with the microbiome of controls [57, 58]. Although these studies lend weight to the idea that human MHC expression affects the composition of the gut microbiota, they cannot be held solely responsible for the onset of disease. Because of the low incidence of BSRC and SpA among individuals who express the HLA-A29 and HLA-B27 alleles, respectively. This points to the importance of additional factors, either genetic or environmental [59–61].

Therapies targeting the gut microbiome

Due to the significant impact of gut microbiome on immunity and metabolism in uveitis, there has been a growing trend toward therapeutic interventions that target the gut microbiome in order to modify disease outcomes. At present, the primary therapeutic approaches comprise antibiotics, probiotics, prebiotics, dietary modifications, and fecal microbiota transplantation (FMT) [62].

Antibiotics

The use of antibiotics in the treatment of gut microbiome dysbiosis is well-established. As previously reported in the literature [4], administration of oral antibiotics demonstrated a reduction in the severity of EAU in mice. This was achieved through modulation of the gut microbiome composition, resulting in an increase in the frequency of Treg cells in the intestinal lamina propria and extraintestinal lymphoid tissues, as well as a decrease in the number of Th1 and Th17 cells, and the level of inflammatory cytokines. The oral administration of broad-spectrum antibiotics starting one week prior to the immune induction of EAU model has the potential to safeguard mice from severe uveitis. This effect is comparable to that observed in germ-free mice, with a reduction in retinal T-cell infiltration and inflammatory cytokine levels in comparison to EAU mice [1, 63]. Furthermore, the oral administration of minocycline a broad-spectrum tetracycline antibiotic has demonstrated anti-inflammatory and immunomodulatory effects. In experimental studies, it has been observed that minocycline has the potential to alter the gut microenvironment of mice with EAU. After treatment with minocycline, the relative abundances of pro-inflammatory bacteria such as *Desulfovibrio*, *Ruminococcus bromii*, *Streptococcus hyointestinalis*, and pathogenic *Spirochaeta* were significantly reduced. In addition, minocycline supplementation can increase the growth of *Parabacteroides goldsteinii*, which has been demonstrated to decrease IL-1β and TNFα levels and maintain intestinal permeability thereby significantly reducing the severity of EAU in mice model [64].

Probiotics

Probiotics are defined as live microorganisms that, when administered in sufficient quantities, can provide a health benefit to the host. The mechanism of action of probiotics is associated with their capacity to compete with pathogenic microorganisms for adhesion sites, exhibit antagonistic effects against these pathogens, or regulate the host's immune response by enhancing Treg cell differentiation. Lactic acid bacteria are one of the most commonly used probiotic strains to improve the intestinal barrier and immune function [65, 66]. The impact of probiotics on the EAU mouse model was studied in which the experimental design involved administering antibiotics to the mice prior to providing them with IRT-5 probiotics, which consisted of a combination of mixture of five strains of lactic acid bacteria that includes *Bifidobacterium bifidum*, *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus reuteri*, and *Streptococcus thermophilus* [10]. The findings indicate that administering IRT-5 probiotics can potentially modulate the clinical manifestations of ocular autoimmunity in comparison to the control group, thereby serving as a viable preventive measure against the onset of uveitis. Therefore, the administration of antibiotics can lead to an immediate reduction of the gut microbiota, which can be followed by the introduction of beneficial oral probiotics, such as IRT-5, to restore the intestinal flora [10, 17]. The achievement of optimal colonization of probiotics in the intestinal tract poses a substantial challenge that necessitates careful consideration [17].

Prebiotic

The prebiotics concept was introduced for the first time in 1995 by Glenn Gibson and Marcel Roberfroid [67]. Prebiotic was described as "a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improves host health". Fructooligosaccharides (FOS), inulin, and galactooligosaccharides (GOS) are recognized as conventional prebiotics that have been shown to have a significant positive impact on human health as a result of their ability to enhance the presence of lactobacilli and bifidobacteria by generating advantageous metabolites, facilitating calcium absorption, mitigating protein fermentation and pathogenic bacteria, reducing intestinal permeability, and augmenting the immune system [68].

Dietary modifications

Various lifestyle factors, including dietary habits, socioeconomic status, physical inactivity, smoking, and environmental factors, have the potential to disrupt the equilibrium of the microbiome ecosystem [69]. Among all these factors, diet is possibly the most crucial, as it may influence both the richness and diversity of microbiota which may as a consequence impact the immune system. For example, a high-fiber diet such

as unrefined cereals, fruits, vegetables, and legumes is believed to enhance the intestinal microecological environment by increasing the gut microbiome's capacity to produce endogenous SCFAs [70]. Moreover, the consumption of plant-based protein has been reported to increase gut-commensal *Bifidobacterium* and *Lactobacillus* which increase the intestinal SCFA levels, while additionally decreasing the pathogenic *Bacteroides fragilis* and *Clostridium perfringens*. Consumption of animal-based protein was found, on the other hand, to increase the number of bile-tolerant anaerobes like *Bacteroides*, *Alistipes*, and *Bilophila* [71, 72]. Research studies in both animals and humans have demonstrated a correlation between high fat diets and reduced richness and diversity of the intestinal microbiota [73]. Additionally, studies have demonstrated that exogenous administration of propionate and butyrate can modulate the immune system and potentially serve as treatment strategies by reducing the severity of EAU in animal models [22, 27].

FMT

FMT, namely stool transplantation, involves the replacement of a patient's original gut microbiome with the entire fecal microbiome of a healthy donor. This procedure aims to modify the microorganism composition within the gut. The utilization of FMT is currently being studied for a diverse range of medical conditions. It has received authorization for the treatment of recurrent colitis induced by *Clostridium difficile* and has demonstrated significant effectiveness in this respect [74]. EAU mouse models developed more severe uveitis after receiving FMT from BD or VKH patients, accompanied by increased IL-17 and IFNγ production. However, there is still not enough clinical evidence to support its use in other conditions like IBD, ankylosing spondylitis, or uveitis because of its substantial interindividual variability [75].

Conclusions

The current literature supports the possible causality between intestinal dysbiosis and immune mediated uveitis. There is still much to learn about the microbiome, and many questions remain unanswered, such as how the microbiome is established in early life, how it is affected by environmental factors, and how it can be manipulated to promote health and prevent disease. The complexity of the microbiome presents challenges in studying and understanding its role in human health and disease, as well as developing effective treatments or interventions. The gut-eye axis, which has been proposed as a potential explanation for the microbiome effect on ocular inflammation and diseases, is not yet well-understood and requires further research. By exploring this area, researchers can expand the current knowledge base and potentially uncover new therapeutic targets for these conditions. In the future, the ability to modulate the composition of the intestinal microbiome through dietary supplementation or the use of certain medications may pave the road for new therapeutic modalities.

Abbreviations

BD: Behcet's disease

BPB: butyrate-producing bacteria

EAU: experimental autoimmune uveitis

FMT: fecal microbiota transplantation

HLA: human leukocyte antigen

IBD: inflammatory bowel disease

IL: interleukin

IRT-5: probiotics consisted of a combination of mixture of five strains of lactic acid bacteria

NIU: non-infectious uveitis

SCFA: short-chain fatty acid

SpA: spondylarthritis

SRB: sulfate-reducing bacteria

Th: T helper

Treg: regulatory T

VKH: Vogt-Koyanagi-Harada disease

Declarations

Author contributions

HA and SS equally contributed to: Conceptualization, Writing—original draft, Writing—review & editing.

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The authors declare that they have no conflicts of interest.

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