The Role of Gut Microbiome in Autoimmune Uveitis

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Abstract

The gut microbiome has important physiological functions and plays an indispensable role in the human body. Currently, there are an increasing number of studies revealing the close correlation between dysbiosis of the gut microbiome and a variety of autoimmune diseases, including autoimmune uveitis. This brief review summarizes recent literature regarding the relationship between dysbiosis and the occurrence and development of autoimmune uveitis. Dysbiosis participates in the pathogenesis of autoimmune uveitis largely by 4 mechanisms: antigenic mimicry, disturbance of intestinal immune homeostasis, destruction of the intestinal barrier, and reduction of beneficial anti-inflammatory metabolites. Further elucidation of these mechanisms will facilitate the treatment of the gut-microbiome-relevant autoimmune diseases by potential therapeutic strategies, such as antibiotics, probiotics, diet modifications, and fecal microbial transplantation.

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Introduction

Uveitis, an inflammatory disease of the intraocular uveal tissues (including the iris, ciliary body, and choroid), can cause serious visual impairment and may also involve adjacent tissues such as the retina, optic nerve, and vitreous body. Uveitis often occurs in young adults; the median age of onset of uveitis is around 35 years. Uveitis accounts for about a quarter of all cases of blindness in developing countries and for 10–15% of preventable cases of blindness in developed countries [1, 2]. About 35% of all uveitis patients have been reported to suffer significant visual impairment or legal blindness. Prompt therapy and rapid control of ocular inflammation are integral to maintaining good visual acuity. At present, the mainstay treatment of uveitis involves the use of ciliary muscle paralysis agents and glucocorticoids (both locally and systemically). Addition of immunomodulatory therapy increases disease remission and limits steroid use. Depending upon its etiology, uveitis may be classified into infectious or noninfectious uveitis; the latter is primarily related to autoimmunity (autoimmune uveitis) [3]. Autoimmune uveitis often comorbid with other autoimmune diseases, such as ankylosing spondylitis, or is

the ocular manifestation of systemic immune diseases such as systemic sarcoidosis, Behcet's disease (BD), and Vogt-Koyanagi-Harada (VKH) disease [4, 5]. An imbalance between autoreactive pathogenic effector T-cells, including T helper 1 (Th1) and Th17 lymphocytes, and regulatory T cells (Tregs), has been implicated in the pathogenesis of autoimmune uveitis. However, the exact mechanism for pathogenesis of autoimmune uveitis remains unclear [6]. Recent studies suggest causative roles of gut microbiota in the development of autoimmune diseases, including uveitis [7].

The microbiota is defined as microorganisms in a specific environment, most commonly the gastrointestinal tract [8]. Gut microbiota refers to all kinds of microorganisms colonizing the intestinal tract, consisting of about 10^{14} microorganisms, whose collective genome is >100 times the size of the human genome [9]. The populations comprised bacteria, fungi, viruses, protozoa, and *Archaea*; bacteria are dominant and largely consist of the phyla *Firmicutes* and *Bacteroidetes* and a lesser number of *Actinobacteria* and *Proteobacteria* [9, 10]. The definition of the microbiome is somewhat ambiguous. Some define the microbiome narrowly as only the collective genomes of the microbiota [11]; others prefer to apply the term to the sum total of the genes and genomes of the microbiota, as well as the products/metabolites of the microbiota and the host environment [12]. We favor the latter definition of the microbiome in this review.

Gut microbiome has many important physiological functions, such as protecting the host from pathogens, promoting digestion and absorption, regulating the function of the immune system, synthesizing vitamins and amino acids, and metabolizing drugs [13]; thus, it is considered an indispensable part of the human body. The microbiome evolves within a healthy host from birth to death, constantly fine-tuning itself to maintain a homeostatic balance with the host's immune system. The evolution of the human microbiome is governed by host factors such as both the adaptive and the innate immune system, as well as external factors such as diet, medication and toxin exposure, and illness [14]. An imbalance of the normal gut microbiota composition is called dysbiosis [15]. Dysbiotic conditions can favor invasion and growth of pathogenic species and can disrupt the finely tuned regulatory circuits of the immune system, thus potentially induce diseases [14]. Indeed, an increasing number of studies have demonstrated that dysbiosis may be closely connected to a variety of diseases, including autoimmune diseases (e.g., ankylosing spondylitis [16, 17], rheumatoid arthritis [18], and multiple sclerosis [19, 20]), inflamma-

tory diseases (e.g., inflammatory bowel disease [18, 21]), neurological diseases (e.g., Alzheimer's disease [9, 20] and Parkinson's disease [22]), and eye diseases (e.g., age-related macular degeneration [23, 24], diabetic retinopathy [25], dry eye [26, 27], and glaucoma [28, 29]). The purpose of this review is to explore the role and mechanism of the gut microbiome in autoimmune uveitis and to propose several potentially effective therapeutic strategies to treat uveitis by targeting gut microbiome.

Correlation between the Gut Microbiome and Autoimmune Uveitis

Over the past 2 decades, experimental data have demonstrated the critical role of the intestinal microbiome in controlling both innate and adaptive immune responses. The strongest evidence of the role of the gut microbiota in disease pathogenesis comes from studies using germ-free mouse models of human autoimmune diseases, including spontaneous ankylosing enteropathy [30], type 1 diabetes [31], autoimmune arthritis [32], and experimental autoimmune encephalomyelitis (EAE; an animal model for multiple sclerosis) [33]. In most of these disease models, the severity and/or incidence of disease are reduced under germ-free conditions consistent with the microbiota being a trigger for disease progression [34, 35]. The notion that dysbiosis may be closely connected to autoimmune diseases is also supported by clinical investigations of ankylosing spondylitis [16, 17], rheumatoid arthritis [18], and multiple sclerosis [19, 20]. Although uveitis is an autoimmune disease, the correlation between the intestine microbiome and uveitis was only gradually established within the last 5-6 years, based on both experimental studies using animal models and clinical observations (shown in Table 1), and further supported by findings that common immunosuppressant drugs used in the treatment of autoimmune diseases have some anti-microbial properties.

It was demonstrated that depleting the gut microbiota attenuates disease severity in mouse models of autoimmune uveitis [36–38]. Two mouse models of experimental autoimmune uveitis (EAU), induced EAU and spontaneous EAU, were used in these studies. Induced EAU is established by active immunization with the retinal protein inter-photoreceptor retinoid-binding protein (IRBP) emulsified in complete Freund's adjuvant, a mixture of mineral oil with heat-killed *Mycobacterium tuberculosis*. Pertussis toxin is given as an additional stimulus in C57BL/6 mice to facilitate disease induction. Induced

Table 1. Major references connecting the gut microbiome with uveitis

Year	Study type	Subjects	Major findings	Ref.
2015	Experimental	R161H/B10.RIII	GF/broad-spectrum antibiotics reduced EAU	[38]
2016	Experimental	B10.RIII EAU	Broad-spectrum antibiotics reduced EAU	[37]
2016	Experimental	C57BL/6J EAU	GF/broad-spectrum antibiotics reduced EAU	[36]
2017	Experimental	C57BL/6J EAU	IRT-5 probiotics reduced EAU	[39]
2017	Experimental	B10.RIII EAU	SCFAs reduced EAU	[68]
2019	Experimental	B10.RIII EAU	Intestinal permeability increased in EAU	[67]
2016	Clinical	12 BD/12 HC	<i>Bifidobacterium</i> and <i>Eggerthella</i> increased and <i>Megamonas</i> and <i>Prevotella</i> decreased in BD	[4]
2018	Clinical	13 uveitis/13 HC	<i>Faecalibacterium</i> , <i>Bacteroides</i> , <i>Lachnospira</i> , and <i>Ruminococcus</i> reduced and <i>Prevotella copri</i> and <i>Streptococcus</i> enriched in uveitis	[43]
2018	Clinical	32 BD/74 HC	Sulfate-reducing bacteria enriched and butyrate-producing bacteria and methanogens reduced in BD	[41]
2018	Clinical	38 AAU/40 HC	7 fecal metabolites increased in AAU	[40]
2019	Clinical	14 uveitis/24 HC	Gut fungal richness and diversity decreased and pathogenic fungi enriched in uveitis	[44]
2020	Clinical	82 VKH/63 HC	Butyrate-producing bacteria, lactate-producing bacteria, and methanogens depleted and Gram-negative bacteria enriched in VKH	[42]

GF, germ-free; EAU, experimental autoimmune uveitis; SCFAs, short-chain fatty acids; BD, Behcet's disease; HC, healthy controls; AAU, acute anterior uveitis; VKH, Vogt-Koyanagi-Harada.

EAU models are generally made in B10.RIII or C57BL/6J mice [5]. The spontaneously uveitic R161H mice express an IRBP-specific T-cell receptor (TCR) transgene on the uveitis-susceptible B10.RIII background. R161H mice have an expanded peripheral population of CD4⁺ T cells specific for IRBP 161–180 peptide and spontaneously develop autoimmune uveitis [5].

It was shown that induced EAU in conventionally housed mice is much more severe than that in germ-free C57BL/6J mice. Germ-free mice had lower numbers of infiltrating macrophages, significantly less T-cell infiltration in the retina, as well as reduced numbers of IFN- γ - and IL-17-producing T cells and increased numbers of regulatory T cells in the eye-draining lymph nodes, suggesting a close association of gut microbiome with EAU [36]. Oral, but not intraperitoneal, treatment of broad-spectrum antibiotics (metronidazole and vancomycin) significantly reduced clinical scores of induced EAU in B10.RIII mice [37]. Oral metronidazole and ciprofloxacin also reduced clinical scores of induced EAU in C57BL/6J mice [36]. These results confirmed the contribution of gut microbiota in the EAU model. Oral gavage feeding of

IRT-5 probiotics (consisting of *Lactobacillus casei*, *Lactobacillus acidophilus*, *Lactobacillus reuteri*, *Bifidobacterium bifidum*, and *Streptococcus thermophilus*) also reduced clinical scores of induced EAU in C57BL/6J mice, supporting that gut microbiota may modulate clinical manifestations of EAU [39]. In addition to these studies based on the classic IRBP-induced EAU model, studies in the R161H spontaneous-EAU model have also suggested a role for the microbiome in the pathogenesis of uveitis. Both rearing R161H mice under germ-free conditions and treating them prior to birth with a combination of broad-spectrum antibiotics (ampicillin, metronidazole, neomycin, and vancomycin) resulted in significant attenuation of spontaneous disease and was associated with decreased frequencies of IRBP-specific T cells in the intestinal lamina propria [38].

There are also several clinical observational studies from Asian countries (Japan, China, and India), comparing the microbiota of uveitis patients with healthy controls, which collectively support conclusions drawn from EAU animal studies. Shimizu et al. [4] studied the gut microbiota of 12 BD patients with uveitis and 12 unaffected

individuals in Japan. They reported increased *Bifidobacterium* and *Eggerthella* and decreased *Megamonas* and *Prevotella* in BD patients, suggesting the dysbiosis may have an association with the pathophysiology of BD [4].

Huang et al. [40] studied the microbiota composition and fecal metabolites in Chinese patients with acute anterior uveitis (AAU) compared with healthy volunteers. They did not identify a difference in gut microbiota composition, but did show that the fecal metabolic phenotype in AAU patients was significantly different from healthy controls. The expression of 7 fecal metabolites (including 6-deoxy-D-glucose 1, linoleic acid, *N*-acetyl-beta-D-mannosamine 3, shikimic acid, azelaic acid, isomaltose 1, and palmitoleic acid) was increased in AAU patients [40]. This group also showed that fecal microbial transplantation (FMT) from patients with BD [41] or active VKH disease [42] into autoimmune uveitis-prone B10.RIII mice significantly exacerbated EAU activity and increased the production of inflammatory cytokines including IL-17 and IFN- γ . These results suggest potential causation between intestinal dysbiosis and noninfectious uveitis. They also reported relative enrichment of Gram-negative bacteria (*Paraprevotella* spp.) and depletion of butyrate-producing bacteria, lactate-producing bacteria, and methanogens in the active VKH patients compared with the control group. These differences were reduced after an immunosuppressive treatment. The presence of *Bacteroides* sp.2.1.33B, *Paraprevotella clara*, *Alistipes finegoldii*, and *Eubacterium eligens* was associated with good response to immunosuppressive therapy. Two microbial marker profiles were established to distinguish VKH patients from healthy controls and to predict the effectiveness of treatment, respectively [42].

Chakravarthy et al. [43] studied the gut microbiota of 13 Indian uveitis patients (including idiopathic and autoimmune uveitis) and 13 healthy controls with similar ethnic and dietary attributes. They reported decreased microbiota diversity and abundance in their uveitis cohort [43]. Notably, they also demonstrated a reduction in the diversity of several anti-inflammatory microbes (including *Faecalibacterium*, *Bacteroides*, *Lachnospira*, and *Ruminococcus*) and an increase in the proinflammatory *Prevotella copri* and pathogenic bacteria *Streptococcus* in uveitis patients [43]. This group also investigated the gut fungal microbiome within this cohort of uveitis patients and similarly observed a decrease in the number of fungal species and diversity index (including Shannon diversity index, Simpson index, the number of OTUs observed, and Chao1 index) in uveitis patients compared with healthy controls [44]. Similar to changes in bacterial mi-

crobiota in uveitis patients, most of the fungal genera enriched in the uveitis patients were opportunistic pathogens. In contrast, the fungal genera enriched in the healthy controls included several genera with anti-inflammatory or anti-pathogenic properties [44]. However, it was not specified whether and at what dosages these patients were taking corticosteroids or immunosuppressives.

The dysbiosis of the VKH patients can be partially resolved by an immunosuppressive treatment, suggesting immunosuppressant drugs may have a direct effect on microbiota [42]. Disease-modifying anti-rheumatic drugs (DMARDs) are a class of drugs indicated for the treatment of rheumatoid arthritis and many other autoimmune disorders including uveitis; DMARDs currently include azathioprine (AZA), methotrexate (MTX), cyclosporine A (CsA), and mycophenolate mofetil (MMF) [45]. All 4 of these DMARDs have both immunosuppressive and anti-microbial properties [46]. AZA is an immunosuppressant agent widely used in the management of inflammatory bowel diseases (IBD) and uveitis [47, 48]. AZA is metabolized in the liver to its active form 6-mercaptopurine, which inhibits maturation of B and T lymphocytes through its activity as an antagonist of purine metabolism, resulting in the inhibition of DNA, RNA, and consequently protein synthesis. AZA can suppress the growth of some bacteria such as *Campylobacter concisus*, *Escherichia coli*, and *Mycobacterium avium paratuberculosis* and affect the secretion of extracellular matrix of *E. coli* to inhibit the formation of biofilm [49, 50]. MTX is a structural analog of folic acid that can competitively inhibit the binding of dihydrofolic acid to the enzyme dihydrofolate reductase, thereby interfering with purine and pyrimidine metabolism and therefore inhibiting DNA and RNA synthesis, DNA repair, and cell division. MTX has been found to be bacteriostatic in vitro against *Staphylococcus aureus* (but not against *E. coli* and *Pseudomonas aeruginosa*) [51].

CsA is a lipophilic cyclic peptide, comprised 11 amino acids and derived from fungi, which selectively inhibits calcineurin, thereby impairing the transcription of IL-2, TNF α , and several other cytokines in T lymphocytes. CsA can disrupt fungal metabolism through calcineurin inhibition and has antifungal activities against *Candida albicans* and *Cryptococcus neoformans*. CsA can also inhibit intracellular multiplication of viruses such as hepatitis C virus and human immunodeficiency virus by binding with cyclophilin [52]. MMF is a selective inhibitor of inosine monophosphate dehydrogenase that interrupts guanosine synthesis. It suppresses T- and B-lymphocyte proliferation, reduces antibody production, and inhibits

transmigration of leukocytes. MMF has been widely tested for treating refractory uveitis [53]. MMF inhibits the synthesis of microbial DNA and RNA by blocking purine synthesis, thus has a wide-ranging anti-microbial property [46]. The fact that all 4 DMARDs widely used for the management of uveitis also have anti-microbial functions is consistent with the conclusion of EAU studies that depleting the gut microbiota can attenuate EAU severity, thus reinforcing the idea that uveitis is associated with dysbiosis of gut microbiome [36–38].

Mechanisms of Autoimmune Uveitis Caused by Dysbiosis of the Gut Microbiome

There are a number of related mechanisms involved in the pathogenesis of autoimmune uveitis caused by the dysbiosis, including immune factors (antigenic mimicry, loss of intestinal immune homeostasis, and destruction of the intestinal barrier) and metabolic factors (shown in Fig. 1).

Antigenic Mimicry (Fig. 1a)

Antigenic mimicry or molecular mimicry is the process whereby autoreactive T cells are generated through cross-reactivity of gut microbial peptides with self-antigens. It is one of the leading mechanisms by which microbiota may induce autoimmunity [54, 55]. Microorganisms mimicking protein structures in their host may have an advantage in escaping immune detection. Such similarities may be due to amino acid sequence homology, but also to shared nucleotide sequences or protein structures [56]. Adoptive transfer of spontaneous-EAU R161H mouse-derived T cells activated in vitro by intestinal contents can induce diseases in many naïve wild-type mice within 6–10 days. This result supports a microbial antigenic mimicry process in the pathogenesis of EAU [38].

Although specific microbial antigens triggering uveitis have yet to be identified, candidate antigens from gut microbiome have been identified for several autoimmune diseases. Neuromyelitis optica (NMO) is a CNS autoimmune disease characterized by immune-mediated demyelination of the optic nerve and spinal cord. Autoreactive humoral and T-cell-mediated immunity against aquaporin 4 (AQP4), a predominant CNS water channel protein, drives NMO pathogenesis. The sequence (p207–216) within the adenosine triphosphate-binding cassette transporter permease (ABC-TP) expressed by *Clostridium perfringens* has 90% homology with the 10-amino

acid sequence of AQP4 T-cell epitope p66–75 [57]. The finding that AQP4-specific T cells in NMO patients showed cross-reactivity to the ABC-TP protein of the indigenous gut commensal species supports a microbiota-related molecular mimicry process in NMO pathogenesis [58, 59]. Microbial cross-reactivity has also been demonstrated in patients with systemic lupus erythematosus. Commensals have been identified in the skin, oral mucosa, and gut of lupus patients and healthy controls that are orthologs of the RNA-binding autoantigen Ro60. Two of these identified commensals, *Propionibacterium propionicum* and *Bacteroides thetaiotaomicron*, activated Ro60-specific CD4⁺ memory T cells from lupus patients [55, 60, 61]. Thus, antigenic mimicry by commensals may be a common trigger of autoimmune diseases including uveitis.

Loss of Intestinal Immune Homeostasis: Imbalance between Th17 and Tregs (Fig. 1b)

Under normal circumstances, antigen-presenting cells in gut-associated lymphoid tissue (GALT) present potential invasive pathogens to helper T (Th) cells, especially Th17 cells, to stimulate their proliferation and secrete inflammatory cytokines such as IL-17, which promote the inflammatory response. On the other hand, the presence of Tregs inhibits excessive immune response and prevents persistent inflammation. Th17 cells and Tregs are always in a dynamic balance and together maintain the immune homeostasis of the intestinal tract. Gut commensals can regulate intestinal mucosal immunity, especially the balance between Th17/Tregs [62]. The dysbiosis of gut microbiome could lead to the loss and destruction of intestinal immune homeostasis, lower the threshold of immune activation, break the balance of Th17/Tregs, and result in a significant increase in Th17 generation and a decrease in Tregs production, which contributes to a variety of enteric and extraintestinal inflammatory conditions, such as uveitis [63]. A recent review summarizing the pathogenesis of BD, including infection and genetic and immune factors, showed that alterations of T-cell balance, especially the expansion of Th1 and Th17 cells and the reduction in Tregs were indispensable to the development of BD. Th17 cells and IL-17 pathways were considered to promote the occurrence and activity of the disease [64].

An imbalance between autoreactive pathogenic effector T cells, including Th1 and Th17 lymphocytes with Tregs, has also been implicated in the pathogenesis of autoimmune uveitis [6]. Oral administration of broad-spectrum antibiotics was able to improve the level of Foxp3⁺ Tregs in the lamina propria of the intestine and extraint-

Fig. 1. Four proposed potential mechanisms of autoimmune uveitis caused by dysbiosis of the gut microbiome. **a** Antigenic mimicry: antigenic mimics in the gut microbiome, which have the highly similar structure or sequence with the autoantigens (e.g., IRBP), could activate retinal-specific T cells in the periphery. Therefore, the activated retinal-specific T cells gain the ability to cross the blood-retinal barrier into the eye to induce uveitis. **b** Loss of intestinal immune homeostasis: the dysbiosis of the gut microbiome could lead to the destruction of intestinal immune homeostasis and break the balance of Th17/Tregs cells in the gut, thus resulting in a significant increase in Th17 cell generation with the increasing secretion of IL-17 and a decrease in Tregs production. The imbalance between Th17 cells and Tregs contributes to uveitis. **c** Destruction of intestinal barrier: the dysbiosis of the gut microbiome

could cause intestinal mucosal inflammation and destroy the intestinal barrier, so as to increase intestinal permeability and make the gut leaky. Microbiota and their products (e.g., LPS and β -glucan) may spread out to the vascular system through the leaky gut, and thus translocate to the eye. If they are trapped or deposited in the uvea, they may become the pathogens and trigger immune responses that cause or exacerbate uveitis. **d** Microbial metabolites: intestinal dysbiosis may cause the absence of beneficial microbiota and the reduction in beneficial anti-inflammatory metabolites such as SCFAs, which can in turn increase the production of Tregs, thus indirectly promote the progression of uveitis. IRBP, inter-photoreceptor retinoid-binding protein; SCFA, short-chain fatty acids; LPS, lipopolysaccharide.

intestinal lymphoid tissues, such as cervical lymph nodes, mesenteric lymph nodes, and spleen, and the proportion of Tregs in the retina also increased, accompanied by the obvious amelioration of inflammatory retinal vascular disruption, while Th1, Th17 cells, and inflammatory cy-

tokines decreased, thus reducing the severity of EAU in mice [37]. All of the above indicate that Th17/Tregs imbalance has a pathogenic effect on autoimmune diseases including autoimmune uveitis and the gut microbiome is a potential trigger that should not be ignored.

Destruction of Intestinal Barrier: Increased Intestinal Permeability (Fig. 1c)

The dysbiosis of the gut microbiome could cause intestinal mucosal inflammation, destroy the intestinal barrier, change intestinal permeability, and contribute to intestinal leakage. Microbiota and their products, such as lipopolysaccharide (LPS) and β -glucan, can spread to the vascular system and migrate to tissues through a leaky intestinal tract. Once trapped or deposited in tissues such as the synovial membrane or uvea, they may become the pathogens of the diseases (arthritis or uveitis) and trigger immune responses that cause or exacerbate arthritis or uveitis [65, 66]. For example, increased intestinal permeability has been reported in patients with ankylosing spondylitis, who also showed dysregulation of intestinal tight junction expression and LPS translocation to the vascular system [16].

During the course of an EAU mouse model, there were many morphological changes in intestinal villi, crypt, submucosa, and muscular layer; the ZO-1 expression and intestinal permeability increased, accompanied by higher expression of anti-microbial peptides such as Reg3 γ , S100A8, and lipocalin-2 in the intestine, indicating the inflammatory state in the intestine [67]. In addition, the degree of intestinal dysregulation, the increase in permeability, and the elevation of lipocalin-2 were persistent and in pace with the severity of uveitis. This is consistent with the early hypothesis that intestinal mucosal inflammation may promote the translocation of microbiota or microbial products through increased intestinal permeability, which eventually caused ocular inflammation directly by affecting the eyes or indirectly through molecular mimicry and immune sensitization.

Microbial Metabolites (Fig. 1d)

Gut microorganisms have the capacity to produce thousands of metabolites, among which short-chain fatty acids (SCFAs), primarily acetic acid, propionic acid, and butyric acid, are the most common. SCFAs are fermented metabolites of dietary fiber produced by microorganisms in the colon, which are beneficial to the body and protective in the animal models of inflammatory disease. It was reported that SCFAs were likely to ameliorate uveitis through 2 mechanisms: one is to increase Tregs in the colon and cervical lymph nodes; the other is to reduce the transport of effector T cells between the intestine and spleen during uveitis [68]. Exogenous SCFA supplementation decreased the severity of uveitis in mice [68], indicating that intestinal disorders may lead to the absence of some beneficial microorganisms that secrete anti-inflam-

matory metabolites such as SCFAs, thus promoting the progression of uveitis. Another study has shown that a unique metabolic phenotype was present in the gut of patients with AAU when compared with healthy controls, and the expression of 7 metabolites (6-deoxy-D-glucose 1, linoleic acid, *N*-acetyl-beta-D-mannosamine 3, shikimic acid, azelaic acid, isomaltose 1, and palmitoleic acid) was significantly elevated in the feces of AAU patients [40]. Previous studies have found that these metabolites were strongly associated with some inflammatory or autoimmune diseases. For example, high levels of *n*-6 fatty acids, particularly linoleic acid, were involved in the pathophysiological process of IBD by stimulating the production of proinflammatory mediators [69]. In non-alcoholic fatty liver disease, derived from the dysregulation of lipid metabolism, linoleic acid and palmitic acid were found to impair mitochondrial function, leading to increased oxidative damage, and mediate selective loss of intrahepatic CD4⁺ T lymphocytes, and ultimately accelerate the progression to hepatocellular carcinoma [70]. Azelaic acid, a by-product of fatty acid peroxidation, was reported to promote chronic depression by modulating autoimmune responses [71]. The specific role of these metabolites in AAU is still unclear and warrants further studies. However, it indicates that the importance of metabolic factors in the pathogenesis of autoimmune uveitis should never be overlooked.

It is worth noting that these theories or hypotheses are not mutually exclusive, but explain the pathogenesis of autoimmune uveitis induced by gut microbiome dysbiosis from different aspects (Fig. 1). On the one hand, dysbiosis results in the destruction of intestinal immune homeostasis, the emergence of immune disorders due to decreased immune threshold, and the reduced production of anti-inflammatory metabolites, and the increase in intestinal permeability leads to the translocation of microbiota and microbial metabolites from the intestine into the vascular system; on the other hand, microorganisms could induce uveitis indirectly by the activation of retinal-specific T cells through antigenic mimicry, or the microbial metabolites may act directly on the eyes to stimulate the development of inflammation. In addition, it has been proposed that extensive and broad extraintestinal migration of immune cells existed [72]. The trafficking of lymphocytes and inflammatory cells from the gut to the eye has been reported in the EAU mice model, where the gut-derived cells related to the severity of EAU were detected in the eye [68]. This may be an essential pathogenic mechanism of uveitis, but it still needs to be determined by further studies.

Therapies Targeting the Gut Microbiome

Since gut microbiome plays such a vital role in the process of immunity and metabolism during uveitis, therapeutic approaches targeting the gut microbiome to postpone diseases, which have been effective in the treatment of diseases like *Clostridium difficile* colitis [73], have gradually become a trend. Currently, the main therapeutic strategies contain antibiotics, probiotics, dietary modifications, and FMT.

The role of antibiotics in the treatment for the dysbiosis of the gut microbiome is obvious. As mentioned in previous studies, oral antibiotics were able to reduce the severity of EAU in mice by altering the composition of the gut microbiome, raising the frequency of Tregs in intestinal lamina propria and extraintestinal lymphoid tissues, and decreasing the number of Th1, Th17 cells, and the level of inflammatory cytokines [37]. It has also been reported that oral administration of broad-spectrum antibiotics from 1 week before the immune induction of EAU model could protect mice from severe EAU, akin to germ-free mice, with retinal T-cell infiltration and inflammatory cytokine levels reduced compared with EAU mice [36].

Probiotics are a kind of microbial component with beneficial function, which promote the proliferation of beneficial microorganisms. Oral probiotic strains can regulate immune homeostasis by enhancing Tregs differentiation [74]. As an approach to maintain intestinal health and treat gut microbiome dysbiosis, probiotics are gaining popularity, the importance of which is gradually being noted by researchers. The effects of probiotics on the EAU mouse model was studied, in which mice were pretreated with antibiotics and provided with IRT-5 probiotics, composed of *L. casei*, *L. acidophilus*, *L. reuteri*, *B. bifidum*, and *Streptococcus thermophilus* [39]. The results revealed that the application of IRT-5 probiotics might regulate the clinical manifestations of ocular autoimmunity relative to the untreated group to effectively prevent the development of uveitis. Thus, it is possible to deplete gut microbiome with antibiotics in a short time and then recolonize the intestine with beneficial oral probiotics (such as IRT-5). However, the method by which maximizing the colonization of these probiotics in the intestine is a significant obstacle still needs to be overcome.

A high dietary fiber diet is considered to improve the intestinal microecological environment by enhancing the ability of gut microbiome to produce endogenous SCFAs. Dietary modifications have been reported in several ophthalmic diseases, such as diabetic retinopathy and age-related macular degeneration. It was confirmed that in-

termittent fasting could remodel gut microbiome, improve bile acid metabolism, promote the production of neuroprotective tauroursodeoxycholic acid, which is a secondary bile acid and binds to retinal TGR5 receptors, and ultimately prevent diabetic retinopathy [25]. Low-fat, low-glucose, or low-fructose diets and some micronutrient supplements could also delay the progression of age-related macular degeneration [23]. In addition, similar therapeutic benefits in uveitis mice could be achieved by balancing intestinal Th17/Treg cells through the addition of exogenous SCFAs or its analogs to their diet [68].

FMT is to replace the original gut microbiome of patients with the whole fecal microbiome of healthy donors, so as to change the composition of microorganisms in the gut. FMT can increase the diversity of the microbiome, promote intestinal function, restore bile acid metabolism, and has a significant effect on eradicating *C. difficile* infection in the treatment of colitis [73]. The role of FMT in the treatment of spondyloarthritis and concomitant uveitis was also demonstrated [75]. However, because of differences in the composition of gut microbiome among healthy individuals, it is not clear which individual microbiome is most advantageous for treating a particular disease, and identifying healthy donors for particular diseases may be a challenge for researchers. Besides, the donor materials also need to be strictly tested to avoid posttransplant complications [76].

Conclusion

The crucial role of intestinal microbiome in the development of noninfectious uveitis has been recently proposed. The major evidences are from animal studies, in which depleting the gut microbiota attenuates disease severity in mouse models of autoimmune uveitis. Clinical studies reported differences in the composition of the microbiota in uveitis patients compared with normal controls. Coinciding with these findings, common immunosuppressant drugs (such as DMARDs) for autoimmune diseases (including uveitis) have some anti-microbial properties. The underlying mechanisms by which the dysbiosis is involved in autoimmune uveitis are not fully understood, but antigenic mimicry, disturbance of intestinal immune homeostasis, destruction of the intestinal barrier, and reduction in beneficial anti-inflammatory metabolites are suggested. Further elucidating these mechanisms is necessary and will facilitate potential therapeutic strategies, including antibiotics, probiotics, diet modifications, and FMT, for the treatment of the gut-microbiome-relevant autoimmune diseases.

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Statement of Ethics

The authors have no ethical conflicts to disclose.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

D.C. and X.F. made the outline of the manuscript. Y.C. edited the English text. X.F., Y.C., and D.C. wrote and finalized the manuscript.

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