The human intestinal microbiome is composed of hundreds of species and has recently been recognized as an important source of immune homeostasis. While dysbiosis, an altered microbiome from the normal core microbiome, has been associated with both intestinal and extraintestinal autoimmune disorders, including uveitis, causality has been difficult to establish. There are four proposed mechanisms of how the gut microbiome may influence the development of uveitis: molecular mimicry, imbalance of regulatory and effector T cells, increased intestinal permeability, and loss of intestinal metabolites. This review summarizes current literature on both animal and human studies that establish the link between dysbiosis and the development of uveitis, as well as provides evidence for the above mechanisms. Current studies provide valuable mechanistic insights as well as identify potential therapeutic targets. However, study limitations and the wide variability in the intestinal microbiome among populations and diseases make a specific targeted therapy difficult to establish. Further longitudinal clinical studies are required to identify any potential therapeutic that targets the intestinal microbiome. (Am J Pathol 2023, -:1–10; https://doi.org/10.1016/j.ajpath.2023.03.004)

Although relatively rare, morbidity from uveitis can be high. The underlying etiologies and triggers for uveitis remain a mystery. Current treatment of uveitis includes corticosteroids and immunomodulatory agents. Despite therapeutic advances in use of biologic agents, especially in the past two decades, recurrence is common, and control of disease can pose many challenges. Therefore, ongoing research to elucidate mechanisms involved in the pathogenesis of uveitis is necessary and may lead to the discovery of novel therapeutic targets. In recent years, there has been growing interest in the microbiome and its potential effects on the immune system. This review summarizes recent literature on the potential gut-eye connection, including both animal and human studies supporting this association, as well as the potential therapeutic strategies involving the microbiome for the treatment of uveitis.

Materials and Methods

A literature review was conducted by searching for a combination of the following terms: uveitis, microbiome, Behçet disease, HLA-B27, autoimmune disease, and Vogt-Koyanagi-Harada in the PubMed database. Both original studies and review articles were included. Articles were limited to the English language and publication from 2000 to present, and were searched using the above criteria from September 1, 2022, through October 1, 2022. Two authors (T.M.J. and N.Z.) selected the articles for inclusion based on relevance and all authors (T.M.J., N.Z., and D.A.G.) agreed.

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reviewed them for final inclusion in this review. Only articles that included information on the microbiome and uveitis or autoimmune disease were included. Additional pertinent references were included in the final literature review.

Microbiome Overview

The term microbiome, coined by Joshua Lederberg and Alexa T. McCray, is defined as a multispecies community of microorganisms (bacteria, fungi, and viruses) that differs from niche to niche in population density and community composition. The microbiome varies from that on the skin, inside the nostrils, inside the mouth, along the esophagus, and along the small intestine. The vast majority of the microbiome is composed of bacteria. The human microbiome plays a major role in maintaining immune homeostasis by imparting normal metabolism and immunity to the host. Human skin, for example, harbors a wide range of microbes that help protect against infection.

The human gut microbiome includes bacteria belonging to around 160 identified species. The most dominant bacteria identified in the normal gut microbiome are subdivided into three major bacterial genera: Firmicutes, Bacteroides, and Proteobacteria. Several species of bacteria in the gut are involved in bile acid metabolism, especially the species that belong to Clostridium. This community is dynamic and is known to vary in normal individuals with age, ethnicity, diet, exposure to chemicals, as well as host genetic variation, as suggested by twin studies. This makes the definition of a normal core microbiome challenging.

Dysbiosis is the term used to describe aberrations from the normal core microbiome. Diet and intestinal-related disease, such as obesity and inflammatory bowel disease, are linked to dysbiosis. However, implicating them in the pathogenesis of extra-intestinal diseases, such as arthritis, muscular dystrophy, multiple sclerosis, vaginosis, fibromyalgia, some cancers, and mental disorders, is much more challenging. Gut microbiota and their metabolites have been implicated as potential modulators of the immune response in inflammatory and autoimmune diseases, including autoimmune uveitis. For instance, several studies that compared bacteria profiles in subjects with uveitis with healthy counterparts showed an overall decrease in diversity, wherein symbiotic bacteria that are anti-inflammatory were enriched in healthy subjects in comparison to the proinflammatory bacteria in the guts of uveitic counterparts. Indeed, it has been suggested that reduced diversity may favor the emergence of pathogenic bacteria that mediate inflammation.

Several bacterial groupings support the notion of immunosuppressive bacteria versus proinflammatory bacteria. One of the most important groups of anti-inflammatory bacteria are the butyrate-producing bacteria (BPB). Butyrate, a short-chain fatty acid (SCFA), is a key microbial metabolite that helps maintain host immune homeostasis. As will be expanded on in a further section, it induces immunosuppressive regulatory T cells via several local and systemic mechanisms. In addition, intestinal butyrate inhibits local proinflammatory cytokines, while circulating butyrate prompts the generation of extrathymic regulatory T cells. It also stimulates the release of mucin, which strengthens and protects the gut epithelial barrier. A deficit of butyrate production, in turn, leads to reduced regulatory T cells and activation of immunopathologic T-effector responses.

Loss of butyrate leads to intestinal epithelium barrier dysfunction and facilitates the expression of various inflammatory components, such as the microbe-associated molecular pattern or pathogen-associated molecular pattern factors, which can adversely affect intestinal epithelial cells. BPB include several bacteria, such as Faecalibacterium, Blautia, Roseburia, Lachnospira, and Ruminococcus, which can all contribute to a beneficial anti-inflammatory response. These were increased severalfold in the microbiota of healthy controls compared with those with uveitis, which suggests their role in modulating an autoimmune response when depleted. Decrease in this group has also been reported in the gut microbiome of patients with other autoimmune diseases, including dry eye, inflammatory bowel disease, and encephalitis-related arthritis.

A second group of bacteria is methanogens. They include Candidatus, Methanomethylophilus species, and Methanoculleus species. Their production of methane is believed to ameliorate oxidative stress injury and can suppress the inflammatory response in various tissues in the body, including the retina. In addition, there are multiple other bacteria that are potentially probiotic (organisms that promote the growth of a host microbiota that confers beneficial effects on the host immune system) and anti-inflammatory, and are enriched in healthy gut microbiota but are of unknown physiological relevance, including lactate-producing bacteria (such as Bifidobacterium species), Bacteroides, Dialister, Dorea, Coprococcus, Oscillospira, Odoribacter, Veillonella dispar, Akkermansia muciniphila, Mitsuokella, and Magasphaera.

On the other hand, sulfate-reducing bacteria are a group of opportunistic pathogens with proinflammatory properties. Prevotella, for example, found in microbiota of uveitic subjects, have the ability to activate retina-specific T cells and thus trigger autoimmune uveitis. They exhibit significant interindividual variation and, according to one study, are especially increased in subjects with a vegetarian-rich diet, such as in Indian populations. Another study, however, did not replicate this finding.

Thus, the microbiome is a balance between bacteria with proinflammatory and anti-inflammatory properties. This approach can lead to new therapeutics for autoimmune diseases by finding methods to restore that balance through increasing bacteria with probiotic and anti-inflammatory
qualities while suppressing those with pathogenic characteristics. However, this specific balance and its impact on disease development is complex and difficult to achieve.

**Proposed Mechanisms**

Four main mechanisms have been proposed to explain the influence of the gut microbiome on the development of autoimmune uveitis, as summarized in several recent reviews. Herein, each mechanism is reviewed briefly and evidence for each of these mechanisms is presented by summarizing supportive murine and human studies. Figure 1 summarizes the four mechanisms and their relationship to the development of uveitis.

**Molecular Mimicry**

Molecular mimicry refers to the development of autoreactive T cells against self-antigens due to activation from exposure of mimicker antigens found in the gut microbiome. Evolutionarily, gut microbials may produce antigens similar to their host cells to escape immune detection. However, when an overactive immune system recognizes such antigens as foreign, autoreactive T cells can develop against host antigens. Molecular mimicry has been implicated in multiple autoimmune conditions, and specific pathogens and antigens have been proposed in diseases such as systemic lupus erythematosus, Guillain-Barré disease, and neuromyelitis optica. In an *in vitro* study, T cells derived from a spontaneous experimental autoimmune uveitis (EAU) model activated by intestinal contents delivered to EAU lymph nodes were able to induce uveitis when transferred intraperitoneally to wild-type mice, supporting the notion that the intestinal contents have activating antigens specific to ocular structures.

**Imbalance of Effector T Cells and Regulatory T Cells**

In a nonpathologic immune state, there is a balance between effector T-helper cells [type 1 helper T cell (Th1) and type 17 helper T cell (Th17)] that promote inflammation and regulatory T cells, which are immunosuppressive. Antigen-presenting cells within the gut lymphatics present pathologic antigens and stimulate Th1 and Th17 to induce an inflammatory response. The balance between these two cell types maintains immune homeostasis. Dysbiosis can lead to an imbalance, resulting in significantly more proinflammatory T cells leading to extraintestinal inflammatory conditions, such as uveitis. Studies that attempt to capture this balance in uveitis typically analyze the concentration of these cell types in gut lymphoid tissues, such as the intestinal lamina propria, and compare this with extraintestinal lymphatic tissues, such as the cervical or mesenteric lymph nodes, as well as concentrations within the ocular structures, such as the retina.

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**Figure 1** Four interrelated proposed mechanisms of the intestinal microbiome that lead to ocular autoimmunity, and the gut-eye axis. Dysbiosis leads to a decrease in short-chain fatty acids (SCFAs), among other intestinal changes. These alterations promote increased intestinal permeability and an imbalance of T cells with an excess of effector T cells and a loss of regulatory T cells. Excess effector T cells are activated by mimicker microbial antigens primed against host ocular antigens (molecular mimicry) and cause uveitis. Increased intestinal permeability leads to translocation of bacterial products to remote host locations (including the eye), causing a nidus of inflammation. Image created with BioRender.com.
Increased Intestinal Permeability

Microbial products, such as lipopolysaccharide, if spread to extraintestinal locations (such as the eye) can become a nidus of inflammation or exacerbate an underlying autoimmune disease. Dysbiosis can lead to a breakdown in the intestinal barrier, causing a leaky system in which bacteria or their products translocate via the vascular system. This may cause direct inflammation or may augment autosensitization by exposing the immune system to antigens that mimic host cells.44,45

Production of Microbial Metabolites

Bacteria in the intestine produce multiple metabolites, including SCFAs, which are thought to be protective from inflammatory disease. The most common metabolites include acetic acid, propionic acid, butyric acid, and valeric acid. The main mechanism by which SCFAs are thought to ameliorate inflammatory disease is by regulating the balance between regulatory T cells and effector T cells. SCFAs regulate gene expression of immune cells and promote or decrease their activity via activation of G-protein—coupled receptors. Julia et al43 proposed that SCFAs stimulate immune tolerance by inducing regulatory T cells and suppressing Th1/Th17 cells in the gut lymphatic tissues. In addition, SCFAs likely influence intestinal integrity. Administration of acetate and propionate in rats decreases duodenal permeability.44 Studies aiming to characterize this effect in uveitis have looked at oral SCFA supplementation and its effect on T cells and uveitis severity, the results of which will be discussed in subsequent sections.

These four mechanisms are clearly not mutually exclusive, but rather they build on one another. For instance, gut antigens that are mimickers can stimulate an immune response, tipping the balance between regulatory and effector T cells, leading to a proinflammatory pathologic state that promotes intestinal permeability and further perpetuates inflammation.

Effect of the Microbiome on Experimental Autoimmune Uveitis

Two models of mouse autoimmune uveitis have primarily been applied to study alterations in the gut microbiome associated with uveitis: the spontaneous and induced models of EAU.45 These models primarily rely on a T-cell response to induce ocular inflammation. The induced model relies on active immunization with a retinal protein, the interphotoreceptor retinoid-binding protein (IRBP), to stimulate an autoimmune response against the host retina. IRBP is given subcutaneously in a mixture of mineral oil and an adjuvant, such as heat-killed *Mycobacterium tuberculosis* or pertussis toxin.42 Administration with the adjuvant is necessary to induce a massive innate immune response to subsequently activate autoreactive host T cells. The spontaneous EAU model, on the other hand, expresses an IRBP-specific T-cell receptor transgene on a uveitis-susceptible mouse strain background. These mice naturally develop T cells to IRBP and thus spontaneously develop autoimmune uveitis regardless of an external trigger.45 In short, one model relies on activation via an introduced antigen, whereas the other is inherently primed to develop inflammation. However, in the spontaneous model, retina-specific T cells must be activated via their T-cell receptor to induce disease. Because retinal antigens are sequestered within the immune privileged eye, the activating antigens must be extraocular, such as the gut microbiome. Given the wide spectrum of human uveitis, certain diseases may be more appropriately analogous to one model over the other.

Both models have been used to study the effect of dysbiosis on uveitis development and have provided evidence for the above four key proposed mechanisms. Many of these studies evaluate the population of regulatory T cells and effector T cells (Th1 and Th17), as well as these cell populations in relation to time of uveitis development and their location (gut lymphoid tissue versus ocular structures) to support a causal relationship.38–42

Nakamura et al46 demonstrated in the induced EAU model that oral broad-spectrum antibiotics (metronidazole, vancomycin, neomycin, and ampicillin) given for 1 week before immunization decreased the severity of uveitis over that of water-treated mice. The i.p. administration of these antibiotics did not attenuate uveitis or alter the gut microbial load, as opposed to oral administration, suggesting the alteration in the gut microbiome as the cause rather than a direct anti-inflammatory effect of the antibiotics. Many antibiotics, such as metronidazole, for instance, are known to be immunosuppressive by themselves.38 Intestinal regulatory T cells were increased as early as 2 weeks after antibiotic treatment, and extraintestinal regulatory T cells were increased at weeks 3 and 4 after treatment.

Other groups have used a variety of antimicrobial treatments and rearing in germ-free environments with similar results. Germ-free mice lack microorganisms and are born and reared in sterile conditions to prevent contamination. New strains and colonies are typically established by a sterile cesarean section and transferred to a germ-free environment with a germ-free foster mother.47 Heissigerova et al40 showed that inflammation was depressed only when treating 1 week before disease development, but not during the development of the disease. This provides further evidence that the preexisting gut microbiome in these mice is important in disease induction rather than an alternate route of inflammatory reduction due to the antibiotic treatment. In addition, antibiotic treatment was less effective at reducing inflammation than rearing in a germ-free environment, in which there is a complete absence of the gut microbiome. Seidler Stangova et al48 used ciprofloxacin and metronidazole in an induced model and found a greater effect of uveitis attenuation the earlier the treatment
The Microbiome and Uveitis

The course and type of antibiotic treatment appear to have significant effect on disease development. In contrast to studies by Nakamura et al., in a separate study using immunized mice treated with long-term broad-spectrum courses of antibiotics, the mice developed fulminant uveitis. In addition, the increased number of regulatory T cells were not observed, as opposed to that reported by Nakamura et al. In this study, antibiotics were given to the pregnant dam and continued indefinitely, a much longer treatment compared with that in the study by Nakamura et al. In addition, in the spontaneous model, individual treatment with each antibiotic separately did not significantly alter disease course compared with combination treatment. This suggests that antibiotic course and specific rearing environments can potentially alter the microbiome in such a way as to either prevent or provoke autoimmunity. Although certain bacterial species promote development of Th17 cells, others promote regulatory T cells, and the antigen responsible for molecular mimicry has not been identified.

Given the heterogeneity of the microbiome across laboratories, there is perhaps no one specific bacteria responsible, leading to the variability in study results. It is not the depletion of a specific organism, but instead alterations of the microbiome composition that influence disease.

Intestinal permeability and the effect of bacterial metabolites have also been studied in EAU. SCFAs are protective in other autoimmune diseases, such as graft-versus-host disease, colitis, and multiple sclerosis, and are thought to decrease intestinal permeability and up-regulate regulatory T cells in the gut. Exogenous administration of propionate was shown in EAU to decrease uveitis severity by inducing regulatory T cells in the intestinal lamina propria and decreasing levels of Th1/Th17 effector cells. In addition, intestinal permeability and intestinal lipocanal production were greatest during peak uveitis in the induced model. Butyrate attenuates intraocular inflammation when administered 14 days after immunization, with an increased number of regulatory T cells and a decreased number of Th17 cells in the draining lymph nodes and spleens of an induced EAU model.

Although such studies support the notion that the gut microbiome influences uveitis development, causation by showing that effector T cells are primed in the gut and subsequently induce ocular disease is difficult. In the induced model, Th1 and Th17 were found in higher concentration in the mesenteric lymph nodes before the development of uveitis, suggesting lymphatic migration of primed T cells from the gut. In a separate study using an induced EAU mice model, in spite of an abundance in pathologic T cells in the eye draining lymph nodes, there was only a small increase in Th1 and no increase in Th17 cells in the gut mesenteric lymph nodes. The authors of this study propose that rather than the gut being the site of T-cell activation, it is perhaps the local skin where immunization occurs, with the gut providing an amplification signal.

However, Horai et al. have demonstrated in the spontaneous EAU model that autoreactive T cells need an activation signal in the lamina propria of the intestine and that large numbers of these activated T cells were found in the gut before the development of disease. As spontaneous EUA mice do not require an administered IRBP antigen for uveitis development, the decreased uveitis severity in depleted microbiome after antimicrobial or germ-free rearing suggests that activation arises from a gut microbiota.
signal. The highest level of evidence for causation was demonstrated by Nakamura et al., who demonstrated traveling of effector T cells from the intestine to the eye in the induced model using a Kaede transgenic mouse model in which gut effector T cells were photoconverted in the colon to allow for detection of these cells after migration to the eye. In total, multiple EAU models have demonstrated both a correlation between the gut microbiome and the development of uveitis as well as evidence for the microbiome being the cause of uveitis severity.

Clinical Studies

It is difficult to draw causal conclusions from clinical studies that aim to characterize dysbiosis of the gut microbiome and its role in modulating immune homeostasis. However, several studies within specific disease populations, such as Behçet disease (BD) and Vogt-Koyanagi-Harada (VKH) disease, have provided a strong association, mainly by comparing the microbiome of individuals with a disease with healthy controls.

Behçet Disease

BD is proposed to develop as a result of a combination of both genetic and environmental factors, such as infectious agents that might lead to immune dysregulation. Aberrant activity of Th1, Th17, and regulatory T cells was observed in patients with BD, and recent studies have shown that the gut microbiome may play a crucial role in modulating the T-cell activity that can induce vasculitis and tissue damage.

There is a significant reduction of the total bacterial diversity in patients with BD compared with healthy controls. The most demonstrated changes were an increase in sulfate-reducing bacteria, _Stenotrophomonas_ species, _Actinomyces_ species, and _Paraprevotella_ species concurrent with depletion of BPB and methanogens. The depleted BPB in patients with BD were _Roseburia_ and _Subdoligranulum_, which belong to _Clostridium_ clusters XIVa and IV, respectively. This lack of balance results in intestinal epithelial barrier damage and facilitates the entry of the effector molecules into intestinal epithelial cells. Some researchers attempted to describe the mechanism through which this induces inflammation in patients with BD by using mice studies and transplantation of feces from clinically active patients to mice. They concluded that the state of immune hyperactivity in patients with BD is the result of a damaged intestinal barrier that allows for the transfer of immune-stimulatory factors. One study took it a step further by randomizing patients with BD to butyrate-enriched diets, and found a decrease in disease activity and corticosteroid use.

The role of oral flora has also been considered in the etiopathogenesis of BD given the high frequency of oral ulcers. Studies show that salivary _Rothia mucilaginosa_ was more abundant in the active BD group in patients with recurrent aphthous ulcers but not in those without. The reason for this, however, is not currently known. A possible association with localized progression and systemic manifestations of BD has been hypothesized.

Vogt-Koyanagi-Harada Disease

Similar to that in patients with BD, the microbial composition of the intestinal microbiome in patients with VKH disease is different from their healthy counterparts. Three enterotypes (Prevotella enterotype, Bacteroides enterotype, and Mix enterotype) were described in patients with VKH disease and healthy controls. In patients with VKH disease, both the Mix enterotype and the Bacteroides enterotype were enriched with Gram-negative bacteria, such as _Bacteroides_ species, _Paraprevotella_ species, _Prevotella_ species, and _Parabacteroides_ species but showed depleted BPB, lactate-producing bacteria, and methanogens. These findings were partially consistent with earlier findings in patients with BD, although most VKH-associated species that were found were specific for this uveitis entity, indicating that each disease may have a unique microbiome composition.

HLA-B27—Related Uveitis

Several studies discussed the idea that HLA-B27 alters the composition of the gut microbiome, making it one of the predisposing factors contributing to the disease process. However, the exact mechanism by which it may cause disease is still poorly understood.

One theory is that dysbiosis alters gut permeability by a mechanism similar to the one discussed previously. This allows for the translocation of bacteria and/or microbial products to regional lymph nodes, which, in turn, triggers a systemic immune response in the form of diseases, such as ankylosing spondylitis and inflammatory bowel disease.

For example, endotoxin, which is a component of Gram-negative bacteria cell walls, binds to toll-like receptor 4, a protein involved in the activation of the innate immune system whose expression is increased in patients with active anterior uveitis.

Microbial peptides, such as those from _Chlamydia trachomatis_, are antigens that bind HLA-B27, which may, in turn, induce an immune response in target organs, resulting in arthritis and even uveitis. Accordingly, this provides evidence that a cross-reactive immune response between peptides derived from gut microbiome and endogenous peptides can lead to the development of anterior uveitis.

It may be of value to study the aqueous humor of patients with acute and recurrent acute uveitis as it may have a unique microbiome not previously recognized. It has always been believed that aqueous humor is sterile, but one study in patients with glaucoma revealed increased aqueous levels of a uremic toxin produced by gut bacteria.
Although the exact pathogenesis was not described, this opens a new door for uveitis research.

Birdshot Chorioretinopathy

Dysbiosis has also been discussed as a possible etiology of birdshot chorioretinopathy because it occurs exclusively in HLA-A29-positive patients, and the previous proposition that HLA may play a role in shaping the gut microbiome. One study analyzed the effect of HLA-A29 on the intestinal microbiome in healthy individuals from two different databases. While HLA-A29 positivity affected the gut microbiome, the specific bacterial composition needs to be determined.

In summary, most clinical studies to date have found an association between disease development and dysbiosis. However, determining causality in these studies is difficult, and the exact pathophysiological meaning of the change in microbiome is unclear.

Therapeutic Approaches

Differences in the microbiome of those with a disease and healthy individuals have been identified. However, extrapolating this to therapeutics is a much more difficult task. Targeting the gut microbiome to suppress autoimmune uveitis can be approached via two broad strategies. The first is to correct the gut dysbiosis by supplementation of good immunosuppressive bacteria via probiotics, elimination of bad proinflammatory bacteria via antibiotic administration, or complete restoration of the gut microbiome through fecal microbial transplantation. The second strategy is to directly supplement with bacterial metabolites, such as SCFAs, to promote regulatory T-cell expression and increase intestinal integrity.

Probiotics are live organisms that, when administered in sufficient quantities, have the ability to change the gut microbiome composition. Administration of probiotic Escherichia coli Nissle 1917 (EcN) has been shown to be effective in reducing clinical symptoms of inflammatory bowel disease. Experimental studies using EAU models have shown promising results in suppressing extra intestinal autoimmune diseases. Dusek et al studied the effect of EcN and E. coli O83:K24:H31 (EcO) oral supplementation on the induced EAU model, and showed that live EcN protects against uveitis development, but EcO does not. However, mice treated with EcO had high mortality, sometimes even before immunization, likely due to virulence factors released by the bacteria in interacting with the host microbiome. This effect of EcO is not commonly reported, and the authors noted that different animal facilities likely harbor different microbiomes. This highlights the fact that these experimental models are likely not generalizable to identify any one beneficial microbe. Interestingly, the protective effect of EcN only occurred if administered before or during immunization, but not after development of uveitis, suggesting that EcN colonization is required to influence the development of autoreactive effector T cells. Administration of EcN decreased gut permeability, and decreased retina-specific T cells in the lymphatics draining the eye and site of immunization. In the gut lymphatics, there was a significant decrease in proinflammatory cytokines (tumor necrosis factor-α, IL-1β, IL-33, and S100 calcium-binding protein A8).

Kim et al evaluated the effect of oral treatment with a combination of Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus reuteri, Bifidobacterium bifidum, and Streptococcus thermophilus (a combination known as IRT-5) immediately after immunization for 3 weeks and noted a decrease in inflammation on retinal histology compared with that in controls. Interestingly, although there was a reduction in autoreactive cytotoxic T cells (CD8+), there was no difference in CD4+ T cells, and a reduction in regulatory T cells in the treatment group after 3 weeks of treatment. This indicated that the modulation of cytotoxic T cells is not regulated by regulatory T cells in this model. However, given that the cervical lymph nodes were sampled at 3 weeks after induction and treatment, it is difficult to draw firm conclusions.

Overall, in addition to the previously described animal models, supplementation with SCFAs has sparse clinical evidence. A small clinical study of 17 patients with BD was performed in which patients were randomized to two separate butyrate-rich diets. In addition to various inflammatory parameters measured after intervention, disease activity and corticosteroid usage decreased in both groups. This proof-of-concept trial was based on previous studies that showed a decrease among Roseburia and Subdoligranulum species, and subsequently, a decrease in fecal butyrate production in the gut microbiome of patients with BD. However, there are no current clinical studies of SCFA administration on uveitis development.

The animal model evidence for antibiotic use in attenuation of uveitis has been discussed above. In addition, a recent article posited that all current immunomodulatory therapies are inherently antimicrobial, and that this may be contributing to their positive treatment effect. Administration of immunomodulatory therapy may alter the microbiome to promote immunosuppression.

Lastly, replacement of the gut microbiome using fecal microbiota transplantation is a proven treatment for Clostridium difficile infectious colitis. It is performed via colonoscopy or administration via nasogastric route. Some animal studies of uveitis illustrate the effect of fecal microbiota transplantation on uveitis severity. Ye et al in their study of the microbiome of patients with BD, transplanted pooled stool samples from patients with BD into an induced EAU model and noted a significant increase in uveitis severity as well as inflammatory markers (IL-17 and interferon-γ). A CD25 knockout mouse model that lacks IL-2 signaling spontaneously develops severe Sjogren...
syndrome with ocular findings of complete lacrimal gland atrophy and a dry eye phenotype. This phenotype was exacerbated if mice were raised in a germ-free environment. However, mice had improved lacrimal gland pathology and decreased disease activity after administration of fecal microbiota transplantation from wild-type mice. Overall, reconstitution of a healthy gut microbiome has the potential to attenuate uveitis severity; however, there is little clinical or animal evidence for its utility.

Conclusions

The link between the intestinal microbiome and uveitis is clear. Human studies have established that the gut microbiome is altered in disease states, and animal models have provided good evidence that dysbiosis is one of the causes of autoimmunity, rather than an association. However, much work needs to be done to translate this into clinical application. First, there is no clear microbial target. Although most EAU studies noted a benefit from broad-spectrum antibiotic treatment or rearing in a germ-free environment, not all did, and the time course and specific antibiotic regimen or target is not clear. Although some generally accepted bacteria are proinflammatory and others immunosuppressive, difficulty in identifying a specific antimicrobial target arises from the microbial variation among populations and diseases. There is not a single organism that is pathologic, but rather a composition that promotes or suppresses autoimmunity, making identification difficult. Supplementation with beneficial microbial metabolites, such as SCFAs, or complete fecal microbiota transplantation may be one potential avenue, but clinical evidence is currently lacking, and further longitudinal patient studies are needed to establish benefit.

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