Research Article

The Link Between Gastrointestinal Microbiome And Ocular Disorders - A Review

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The gut-eye axis has been hypothesised to be a factor in many eye pathologies. This review examines numerous papers from PubMed about this topic. Bacterial commensals could either be protective by regulating the immune system or prove to be damaging to the gut mucosal wall and incite an inflammatory process. The balance between the two appears to be crucial in maintaining eye health. Uveitis seems to be the most studied link. However, retinal conditions and recently glaucoma have been implicated in such process. The use of probiotics, dietary modifications, antibiotics, and FMT in mice with pathologies like those encountered in our practice, appears to halt the ocular disease course or at least prevent its progression. Clinical trials are currently underway to investigate the clinical significance of diseased patients.

Introduction

The field of ophthalmology is among the fastest developing areas in medicine. Numerous pathologies are investigated for possible inciting factors with well-established diseases to tailor appropriate management protocols. One of the potential triggers is the gut microbiota. Changes in gut microbiota composition, as evidenced from stool samples of patients with eye pathologies, are recognised to be correlated with ocular inflammation[1]. In this article, we explore different mechanisms believed to be responsible for this, possible treatment modalities, and how a holistic approach to various ophthalmic conditions could potentially alter patient health outcomes.

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Methods

On June 6th, 2022, a retrospective search on PubMed was carried out using the terms "ophthalmology", "gut", and "microbiome". This displayed a total of 193 papers. 67 of which were deemed relevant for this paper. These papers were mainly concerning uveitis, retina, and glaucoma. They were thoroughly examined, and 55 papers were selected for this article. The literature chosen presents confirmed associations between gut microbial compositions and eye disorders through analysed stool samples. The chosen articles also illustrate studied mechanisms by which inflammation could be driven by gut microbiota in animal models. In addition, they include proposed and proven therapies based on animal models as well.

Review

The Gastrointestinal Microbiome

The gastrointestinal tract is one of the most significant interfaces between the environment and the human host. It houses 70% of the immune system with a diversity of micro-organisms[2]. The gut microbiome refers to the pooled genome of symbiotic and pathogenic micro-organisms inhabiting the gut. These include bacteria, viruses, fungi, and archaea. Interestingly, bacteria housed in the gut contain more genomes than all cells in the body combined[3]. Microbes are variably distributed in the gut, with the colon harbouring the highest diversity and abundance of micro-organisms[3]. As you move further along the gastrointestinal tract, anaerobes become the predominant commensals. Firmicutes and Bacteriodetes phyla make up 80-90% of the entire gut microbiome. Clostridium genus represents 95% of Firmicutes. The Bacteroidetes phylum mainly consists of Bacteroides

and Prevotella[4][5]. Their role has been poorly understood and implicated primarily in pathologies localised to the gastrointestinal system. It has come to light recently that this ecosystem is linked to both innate and adaptive immunity, with a potential impact on eye health[6].

The Gut-Eye Axis

Numerous emerging evidence suggests a possible link between gut microbiota and other bodily systems, namely the brain and the eyes. The notion of the gut-eye axis has been recently proposed whereby changes in gut microbiota have demonstrated an effect on ocular health and possibly an

inciting factor to various pathologies[7]. Though not fully understood, several theories explain this idea. These include the T-cell threshold, leaky gut, and molecular mimicry models. In addition, the complement system and genetic defects, namely HLA-B27, have been proposed to influence the inflammatory process[8]. It is essential to bear in mind that while the correlation between gut dysbiosis and eye pathologies exists, these models do not always provide definitive answers regarding their pathogenesis.

The T-cell threshold model puts forward a practical viewpoint in which certain bacteria can kick-start inflammation. If the dominant bacteria were pro-inflammatory, following the imbalance between gut commensals, T-helper cells can be activated and thus be a key in driving the pathogenesis of uveitis. Several studies have linked Bacteroidetes to uveitis, namely Behçet's disease and Sjögren's syndrome[1][9][10].

The leaky gut model suggests microbial constituents can migrate into the bloodstream, possibly through a damaged mucosal barrier. Laboratory analysis of aqueous humour confirmed the intraocular gut microbiota, which now opens many avenues for us to explore the implications of such findings[11].

Ocular Immune Privilege

It has come to our understanding that the eye is unique because it holds features that, in theory, prevent an immunological response. These include a blood-retinal barrier (BRB) and a lack of direct lymphatic drainage[12]. So how do gut microbiota travel to the eye? One possible explanation is molecular mimicry. The immune system recognises antigens by T-cell receptors and antibodies. While this process is specific, it is not confined to a single antigen. Hence, gut microbiota may exhibit similarities to self-antigens found in other bodily systems, potentially triggering an autoimmune cascade[13].

Anterior chamber-associated immune deviation (ACAID) is a component of the ocular immune privilege. It is an immunological response to antigen entering the anterior chamber. This leads to systemic suppression of potentially damaging cell-mediated and humoral responses that might damage sensitive ocular tissue. For this to happen, transforming growth factor-Beta (TGF-B) in aqueous humour induces the development of F4/80+ monocytes, which phagocytose the antigen. This antigen-presenting cell (APC) travels through the trabecular meshwork and into the venous system reaching for the spleen. Here, it induces the development of regulatory T-cells (Treg) that inhibit T-

helper cells. Therefore, an intact spleen is required for ACAID to function[14][15]. However, adequate immune stimulation can overcome this immunoregulatory environment[16].

Uveitis

The uvea is comprised of the iris, ciliary body, and choroid. Uveitis is an ocular inflammatory disease that can arise from autoimmunity or when the immune system fends off infection. However, the immune system can also attack healthy eye tissue. These are possibly seen because of the leaky gut and molecular mimicry models. Both models share a common factor: the involvement of a specific subset of T-helper cells, Th17, as evident by animal models[17].

Behcet's disease (BD) is an immune-related disease of undetermined cause. It is characterised by recurrent oro-genital ulcers, mucocutaneous lesions, and severe organ involvement. It has been previously linked to stress and environmental factors[18]. Genetic predisposition with HLA-B51 has been investigated, but the link remains unknown[19]. The gut microbiome of patients inflicted with this disease displayed considerable changes when stool samples were analysed. Stool samples were enriched with *Parabacteriodes*, sulphate-reducing bacteria *Bilophila* and *Desulfovibrionaceae* species. In addition, it was also noted that butyrate-producing bacteria Clostridium and methanogens were reduced[20]. Transplantation of BD faeces in mice illustrated remarkable results in which gut integrity was breached, due to decreased expression of tight junctions, with the subsequent effects of experimental uveitis[21].

Sjogren's syndrome (SS) is an autoimmune disorder targeting lacrimal, salivary glands, and other bodily systems. It classically leads to dry eyes (DES) that sometimes can be refractory to conventional treatment. They have been linked to auto-reactive antibodies, particularly anti-SSA/Ro and anti-SSB/LA. Several clinical studies have correlated gut dysbiosis to SS and DES. The common finding was an increase in *Bacteriodetes*, an opportunistic commensal, and a decrease in *Firmicutes* and *Faecalibacterium*. The latter two gut commensals have been observed to produce short-chain fatty acids (SCFA), such as butyrate, which modulates microglial maturation or Treg cells[22]. Gut microbiota has a role in regulating the balance between Th17 and Treg cells. This was evident when germ-free mice were colonised with SS bacteria resulting in decreased Treg cells[23]. One study concluded that the degree of dysbiosis partly correlated to the severity of the ocular surface disease[24].

HLA-B27 spondyloarthropathies (SpA) are a spectrum of disorders that overlap. These include ankylosing spondylitis, reactive arthritis, psoriatic arthritis, juvenile idiopathic arthritis, inflammatory bowel disease, acute anterior uveitis, and undifferentiated SpA[25]. They are one of the more classic examples of how gut dysbiosis affects the eye due to the number of extensive studies being carried out. From recent studies, segmented filamentous bacteria (SFB) have been illustrated to be a common culprit in initiating an arthritogenic reaction. Th17 response, induced in the mesenteric lymph nodes by dendritic cells, in such patients specifically targets SFB resulting in a breach in the mucosal barrier[26]. This is not the first-time micro-organisms have been linked to autoimmunity. Salmonella, a pathogenic gram-negative bacterium, has been well studied and is an excellent example of how a microbe strongly correlates to reactive arthritis and, subsequently, uveitis[27]. This is thought to result from cross-reactivity between HLA-B27 and pathogenic surface antigens[28]. Other enteric gram-negative pathogens, which mimic HLA-B27, associated with SpA and uveitis include Shigella, Chlamydia and Yersinia[29].

HLA-B27 SpA, SS and BD have shown the most significant correlation between gut dysbiosis and uveitis. Other examples with positive correlation include Vogt-Koyanagi-Harada syndrome (VKH) and Birdshot chorioretinopathy[30][31]. However, they are not as extensively explored. This favours a potentially strong relationship between uveitis and gut dysbiosis and paves the path for future research opportunities.

Retina

The retina houses neurosensory photoreceptors crucial for converting light energy into signals carried to the brain to form an image. Gut dysbiosis has been attributed to various retinal pathologies, with proposed mechanisms discussed previously.

Type 2 diabetes mellitus (T2DM) is a chronic, multisystem metabolic disorder with an increasing prevalence worldwide. It is of great interest to the practising ophthalmologist as it leads to diabetic retinopathy (DR), a significant cause of blindness[32]. Adipose tissue, from increased body habitus, drives the process of chronic inflammation, which is the leading cause of insulin resistance[33]. But now, gut dysbiosis may play a role in the disease pathogenesis. It has been found that Bacteroidetes, again the typical culprit, can break the gut mucosal barrier and enter the bloodstream, with low SCFA contributing to the inflammation. In addition, it was also noted that *Bacteriodetes* produce

lipopolysaccharides (LPS) which are interestingly offensive to the gut mucosal barrier and play a role in retina inflammation by increasing interleukin-6 (IL-6)[34][35][36].

Age-related macular degeneration (ARMD) is another leading cause of blindness in western countries, mainly affecting the elderly. ARMD is thought to occur from defects in the complement system, most notably attributed to the complement factor H (CFH) gene[37]. Again, gut dysbiosis has been linked to ARMD and can lead to inappropriate complement activation, a potential influencer of the gut-eye axis, as stated before[38]. Furthermore, one of the landmark studies in ARMD, the age-related eye disease study (AREDS), has demonstrated that antioxidant and mineral supplementation, including zinc, has been shown to reduce disease progression. Zinc absorption may be affected by gut microbiota composition[39].

Other newly discovered areas in which gut dysbiosis has been associated with retinal pathology include retinopathy of prematurity (ROP) and retinal artery occlusions (RAO)[40][41]. These favour healthier guts being protective and how gut dysbiosis could be an approved risk factor besides prematurity and vasculopathy, respectively.

Glaucoma

Glaucoma is an optic neuropathy characterised by progressive visual field loss due to the death of retinal ganglion cells (RGC). It is the leading cause of irreversible blindness worldwide. Raised intraocular pressure is the most important modifiable risk factor. Hence, most management focuses on bringing it down to an acceptable range. Unfortunately, this approach is not enough in most cases. This is mainly due to other risk factors being in play which we cannot control, such as age, race, family history and eye morphology. While we were able to identify some risk factors, others remain to be uncovered[42].

The gut microbiome plays a crucial role in building and maintaining the BRB. While specific good commensals regulate this, other opportunistic microflora can prove to be damaging to it. Heat shock proteins (HSP) are found virtually in eukaryotic and prokaryotic cells. They are produced in response to stress by bacteria in the gut. HSP27 and HSP60 trigger inflammation that activates T-cells, which are pre-sensitised by the microflora, leading to microglial damage. Since microglia are known for their neuroprotective function, this leaves the RGCs exposed to neurodegeneration. Since the specific

HSPs have been identified, further research to develop a future targeted therapy could be on the way[43][44][45].

Future Therapies

Probiotics allow some bacterial gut commensals with anti-inflammatory properties to thrive in the gut environment. Sometimes probiotics compete against pathogens and allow immune system modification by dampening autoimmunity in the eye[46][47]. The IRT-5 regimen includes *Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus reuteri, Bifidobacterium bifidum*, and *Streptococcus thermophilus* has demonstrated such effect[48]. This is clinically significant in the cases of autoimmune dry eye, as evident by a study on mice which illustrated improvement in tear secretion after treatment with the IRT-5 regimen. This was due to the downregulation of APCs in the immune network[49]. In addition, Bifidobacterium promotes the isolation and utilisation of SCFAs, therefore regulating gut m mucosal immunity[50]. This is highly promising as it creates a new approach to treating inflammatory eye pathologies. However, these formulations are currently challenging to implement in our management due to high variations in the strains they contain[51].

Dietary modifications with SCFA administration attenuated uveitis severity through Treg induction in intestinal lamina propria[52]. SCFA also reduce intraocular inflammation induced by LPS[53]. Dietary modifications appear to impact retinal disorders potentially associated with gut dysbiosis. It has now come to light that mice fed with a high glycemic diet developed a disease like that of dry ARMD. When reverted to a low glycemic diet, this arrested the progression of the disease and, in some instances, reversed it. A cluster of Clostridiales was associated with a high glycemic index, while Bacteroidales was associated with a low glycemic index, further supporting the gut-retinal axis hypothesis[3][54]. Moreover, a high-fat diet has been implicated in DR and ARMD. This resulted from bioactive lipids upregulating pathologic retinal angiogenesis, altering the inflammatory response, and affecting both the complement and coagulation cascades[55].

A combination of oral antibiotics consisting of ampicillin, neomycin, metronidazole, and vancomycin can significantly reduce gut *Firmicutes* and *Bacteroidetes*. Furthermore, they increase the number of lymphoid tissue and retina Treg cells. Therefore, modulating the gut microbiome can potentially reduce the disease severity of autoimmune uveitis[56]. Vancomycin decreases the Th17 population in the small intestines of mice, whereas the combination of antibiotics decreased Th17 frequency in

mesenteric lymph nodes[57][58][59]. Oral minocycline is a broad-spectrum antibiotic that provides anti-inflammatory, anti-apoptotic, immunomodulatory, and neuroprotective benefits[60][61]. Oral minocycline has also been shown to increase the number of good bacterial commensals in the gut and potentially reduce the severity of autoimmune uveitis[17][62].

In faecal microbiota transplant (FMT), a diseased person gets their gastrointestinal tract transplanted with a healthy person's stool via colonoscopy. Along with probiotics, they repopulate target gut microbiota and reduce the severity of uveitis[63]. FMT can reverse disruptions to the gut barrier and inflammation affecting the retina, potentially improving the outcome of ARMD[64]. Interestingly, there is a report of a patient who underwent FMT for Clostridium difficile infection, which happened as well to have SpA and psoriatic arthritis, witnessed an improvement in her arthritis[65]. Trials are currently underway to investigate the potential benefits of FMT on SpA, psoriatic arthritis, and rheumatoid arthritis (RA), which are all known to be associated with uveitis[66][67][68]. Regarding SS, a study observed that mice with a similar disease improved ocular surface homeostasis post-FMT transplantation. The reversal of the dry eye in these mice was attributed to reduced T-helper cells in the lacrimal gland[69].

Conclusion

It is early to be assertive of causation here. However, gastrointestinal microbiome composition appears to be correlated to eye health. There seems to be an interplay between leaky gut, molecular mimicry, and T-cell threshold theories in driving the pathogenesis of ocular diseases through an inflammatory process. Various conditions have been implicated, with uveitis appearing to be the most studied disease and one with the most vital link to gastrointestinal microflora. Emerging therapies about dietary modification, probiotics, antibiotics, and FMT are being investigated with promising results that could alter the treatment process of many eye patients.

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