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Does the microbiome cause B27-related acute anterior uveitis?

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Abstract

The microbiome is strongly implicated in a broad spectrum of immune-mediated diseases. Data support the concept that HLA molecules shape the microbiome. We provide hypotheses to reconcile how HLA B27 might affect the microbiome and in turn predispose to acute anterior uveitis. These theories include bacterial translocation, antigenic mimicry, and dysbiosis leading to alterations in regulatory and effector T cell subsets.

Keywords

uveitis; ankylosing spondylitis; HLA B27; microbiome; spondyloarthropathy

INTRODUCTION

If you like reading detective novels, we submit that you should be intrigued by a real life mystery: why does the HLA B27 antigen predispose to developing acute anterior uveitis? In terms of police work, this must be considered a “cold case”; the conundrum was first described in 1973 [1]. And there is no lack of clues; besides HLA B27, there are additional genetic factors [2,3]. We know that the disease is episodic [4]. Some studies have suggested that the disease is seasonal [5]. We know that when one eye flares, the other eye is usually uninflamed [6]. We know that the intraocular pressure typically falls in the affected eye [6]. We recognize an association with spondyloarthropathies including ankylosing spondylitis [6], reactive arthritis [6], psoriatic arthritis [7], and the arthritis of inflammatory bowel disease [8]. We know the function of HLA class I molecules. We know that there are more than 100 subsets of HLA B27 [9] and we know the amino acid sequence for each of the B27 subsets. We know that there are specific infections like Salmonella [10] and Shigella [11] that trigger reactive arthritis. There is even sex to intrigue the reader of this mystery novel since we know that non-gonococcal urethritis is a clear trigger for reactive arthritis [12]. And with this abundance of clues, we are basically completely befuddled. Many theories have been proposed [13]. Virtually none offers a definitive solution for any aspect of HLA B27-related diseases, but the iritis in particular is arguably the most mysterious aspect of all.

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THE MICROBIOME

When four decades of research have failed to solve a puzzle in pathogenesis, a new and seemingly unrelated insight can stimulate a novel perspective. Emerging discoveries related to the microbiome might qualify as the innovation that allows the mystery to be solved at last.

The Nobel laureate, Joshua Lederberg, suggested the suffix, “omics” for many large databases including that needed to catalog the microbiome, the collection of microbial life that shares the human body [14]. We share our bodies with 100 trillion bacteria along with viruses, yeast, and occasionally helminths.

The importance of the microbiome can be appreciated by eliminating it, i.e. raising a mouse in a germ free environment. In the absence of the bacterial stimulation that characterizes colonization of the gut, the spleen and mesenteric lymph nodes never reach their normal size [15]. The immune response is impaired. The symbiosis between bacteria and mammals includes the role of the bacteria to metabolize all food which is ingested, synthesize vitamin K, and produce neurotransmitters. The ability to catalog the microbiome has become feasible because the cost to sequence nucleic acids has fallen exponentially.

Since the microbiome educates the immune system, it follows that the microbiome would influence susceptibility to a variety of immune-diseases. The microbiome is reportedly altered in spondyloarthropathies or diseases associated with spondyloarthropathy including Crohn’s disease [16], ulcerative colitis [17], psoriatic arthritis [18] and ankylosing spondylitis [19]. Table 1 provides a representative list of diseases for which evidence supports a causal role induced by the microbiome.

Our own data derived from the study of rats which are transgenic such that they express human HLA B27 and beta 2 microglobulin indicate the B27 shapes the gut microbiome [20]. Data from transgenic mice which express HLA DR0401 [21] and data from infants who are HLA DQ2 + and at risk for celiac disease [22] also support the concept that HLA molecules shape the microbiome. HLA genes are the most polymorphic of any known genetic system. A plausible hypothesis is that this diversity minimizes the risk that an infectious agent will completely destroy the human race.

HOW DOES THE MICROBIOME RELATE TO ACUTE ANTERIOR UVEITIS

If indeed HLA molecules affect which bacteria predominate in the intestine, we still would require a theoretical framework to explain why this alone would result in acute anterior uveitis. We propose 3 hypotheses which are not mutually exclusive. There are data to support each hypothesis.

One theory is that the bacteria affect the permeability in the gut. This in turn allows translocation of bacteria or bacterial products from the intestine to mesenteric lymph node, spleen, lymph and blood. Increased bowel permeability has been reported in ankylosing spondylitis [23,24], although not every study has supported this conclusion [25]. In the closely related disease, reactive arthritis, bacterial products from the inciting bacteria have been

detected in the joint [26,27]. We have reported that endotoxin, a major component of the cell wall of Gram-negative bacteria, will alter the vascular permeability of ocular vessels in laboratory animals even when it is injected in the footpad, nowhere near the eye [28,29]. If a bacterial product became trapped in the iris or in synovium, it could activate the innate immune response and cause transient inflammation. Or it could in theory become the target of an adaptive immune response and result in more prolonged inflammation [30]. The theory of bacterial translocation helps to explain the overlapping symptoms of ankylosing spondylitis, reactive arthritis, Crohn's disease, and ulcerative colitis. It provides a causal role for HLA B27. However, the translocation of bacterial products to the iris has not been proven, since it is almost unheard of to have access to iris tissue during an episode of AAU. Furthermore, increased gut permeability has been reported in a variety of diseases including diabetes [31]. And bacterial products are common in the joints of patients with rheumatoid arthritis [32].

A second theory holds that a bacterial product mimics an ocular antigen and this provokes an immune response. Mimicry is widely accepted as a potential cause of immune-mediated disease. It is the most accepted mechanism to explain rheumatic fever [33] and it might account for post infectious Guillain-Barre Disease [34]. The laboratory of Rachel Caspi has studied a transgenic mouse whose T cells predominantly respond to a retina derived antigen. This disease is markedly ameliorated by either broad spectrum oral antibiotics or raising the mice in a germ free environment [35]. Further, bacteria from the intestine of these mice can activate the retina-directed T cells but not other T cells, suggesting that the activation requires mimicry [35]. This theory has strong support in the laboratory, although the actual bacteria responsible for the mimicry have not identified. The laboratory data relate to a model of predominantly retinal inflammation, not anterior uveitis. The data do not readily explain an episodic model. Research based on the analysis of sequences maintained in a database concluded that HLA B27 might be unique in how frequently a six amino acid sequence present in B27 might also appear in specific bacterial products [36,37].

Finally, the effect of the microbiome might be to alter the immune response such that acute anterior uveitis is more likely. Clearly gut bacteria influence the number of T cells that synthesize interleukin 17 [38] and the number of regulatory T cells that express the transcription factor FoxP3 [39–41]. These types of effects play a role in mouse models of inflammation such as asthma [39] and arthritis [38]. We have studied the model of T cell mediated panuveitis known as experimental autoimmune uveitis. We have reported that this disease can be ameliorated by broad spectrum antibiotics and these antibiotics induce changes in the number of regulatory T cells (Nakamura, Y, Metea, C, Gruner, H, Asquith, M, Planck, S, Rosenbaum, JT, Lin, P, Altering the gut microbiota ameliorates experimental autoimmune uveitis, Invest Ophthalmol Vis Sci, 55:2497, 2014, abstract).

IF THE MICROBIOME CONTRIBUTES TO ACUTE ANTERIOR UVEITIS, WHAT IS ITS RELATIVE IMPORTANCE AND WHAT THERAPEUTIC STRATEGIES EMERGE?

Diseases result from a mixture of genetic, environmental, and stochastic factors. It is difficult to dissect the relative role of each in any given disease. In two different rodent models of colitis and spondyloarthropathy, a germ free environment will markedly ameliorate both the bowel and joint disease [42,43]. These observation would suggest that the microbiome plays a major role in the pathogenesis of spondyloarthritis. An extrapolation is that manipulation of the microbiome would have a marked effect on the frequency and intensity of acute anterior uveitis.

The microbiome could be altered by a variety of strategies. Antibiotics change the microbiome but the effect is transient and resistant bacteria quickly develop. Fecal transplants have had some therapeutic success in the treatment of ulcerative colitis [17], but their benefit presumably requires repeated re-exposure to the beneficial bacteria. The ideal time to alter the microbiome might be at birth, making sustained alteration of a well-established microbiome very complex. Probiotics are a popular option although little is actually known about how effectively probiotics actually succeed in changing the microbiome. Diet has the potential to alter the microbiome profoundly. Diet, however, is complex and the analysis of a single variable is rarely accomplished. If indeed the microbiome leads to acute anterior uveitis via a change in bowel permeability, epithelial integrity in the intestine might be restored as a therapeutic strategy, regardless of the bacterial milieu [44]. Sulfasalazine might prevent attacks of AAU in part because it reduces the bacterial load in the gut and in part because it inhibits prostaglandin synthesis in the bowel and therefore reduces bowel permeability [45].

In summary, the mechanism by which HLA B27 predisposes to acute anterior uveitis has been a mystery for more than 40 years. The recognition that the microbiome shapes the immune system has emerged with the characterization of the microbiome. The microbiome is a prime suspect to explain the pathogenesis of B27-related acute anterior uveitis.

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Table 1

Representative conditions in which the microbiome has been implicated

Ankylosing spondylitis
Anxiety
Asthma
Atherosclerosis
Colon cancer
Crohn’s disease
Diabetes
Drug metabolism including acetaminophen and cyclophosphamide
Irritable bowel syndrome
MALT lymphoma
Metabolic syndrome
Multiple sclerosis
Non-alcoholic steato-hepatitis
Obesity
Peptic ulcer disease
Psoriatic arthritis
Rheumatoid arthritis
Starvation
Ulcerative colitis
Uveitis