



The Impact of Human Microbiota in Ocular Inflammation



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Abstract

Microbiota corresponds to the microbial associates that exist in the human body, and the genes they encode, the microbiome. Recent advances in genetic techniques are contributing to a better microbiota characterization. Imbalance in the intestinal microbiota - dysbiosis - is associated with several pathologies and reveals its important role as immunomodulator. These developments are particularly significant in ocular immunology, revealing physiopathologic mechanisms and identifying potential therapeutic targets.

Introduction

An immeasurable amount of commensal microbes colonize the skin and mucosal surfaces. Together, the microbial associates that exist in the human body constitute the microbiota, and the genes they encode, the microbiome (Table1) [1]. Referred to as our “forgotten organ”, the microbiota appears to play a major

role in health and disease [2]. Recent advances in next generation sequencing (NGS) technology have enabled to characterize the human microbiota, with unprecedented resolution, and to identify possible related etiopathogenic mechanisms [3]. In this review, the authors give an overview of the current understanding of the microbiota and its potential impact on ocular health.

Table 1: Terms commonly used in the study of the microbiota [25].

Term	Meaning
Dysbiosis	Microbial imbalance
Enterotype	Stratification based on the intestinal microbiota
Microbiome	Collection of the genomes of the microorganisms found on the host
Microbiota	Community of microorganisms found on the host
Probiotic	Dietary supplement containing live beneficial bacteria

Factors Affecting Normal Microflora

Commensal microflora or microbiota consists of the microorganisms present on body surfaces covered by epithelial cells. These micro-organisms co-evolve with their hosts, however, under specific conditions they can overcome protective host responses and exert pathologic effects [4]. Several factors are known to favor the growth of relatively aggressive resident bacteria at the expense of beneficial commensals, leading to dysbiosis. Among them are aging, diet, antibiotic use patterns, exercise, smoking, public health measures and infections [5-7].

Intestinal Permeability and the Microbiota

Dysbiosis seems to modify intestinal mucosal permeability. The interaction between intestinal microbiota and the mucosal

wall is mediated by the same receptors which can recruit effector Th cells and activate innate immunity ensuing inflammation [8]. Zonulin modulates the permeability of intestinal tight junctions and consequently is a marker for enhanced intestinal permeability. Lamprecht, et al. [9] showed that probiotic supplementation decreased Zonulin in feces adding more information on the dysbiosis role on increased intestinal permeability [9]. Accordingly, increased intestinal permeability is associated with autoimmune disease including ankylosing spondylitis, multiple sclerosis and autoimmune hepatitis [10-12].

Microbiota and Systemic Autoimmune Disease

It is theorized that dysbiosis may facilitate autoimmunity at both barrier sites and internal organs. Complex interactions

between genetics, environment, and the microbiota outline the inflammatory status and this encroaches autoinflammatory and autoimmune diseases [13]. Several animal models support a connection between intestinal bacteria and arthritis. On the one hand, germ-free rats developed severe joint inflammation in an adjuvant-induced arthritis model when compared to conventionally raised controls, suggesting that the gut microbiota may have important immunosuppressive effects [13]. On the other hand, it was reported the proarthritogenic role of *Bacteroides* species when introduced into germ-free arthritis-prone rats [14] (Figure 1).

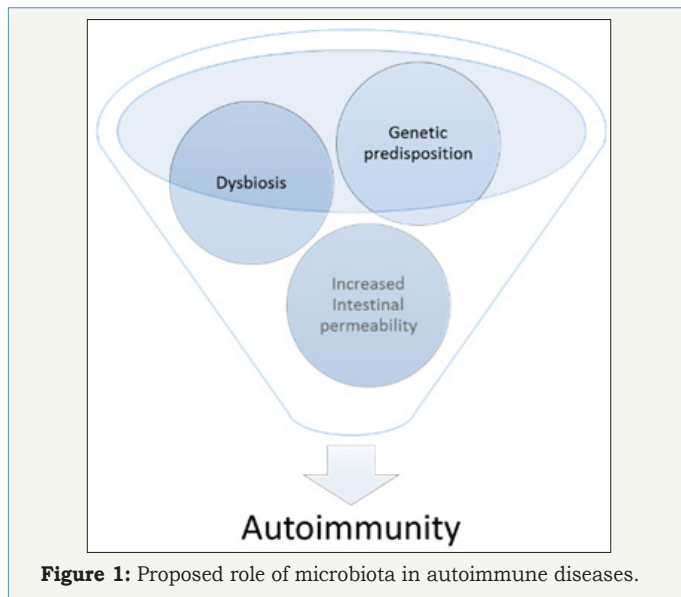


Figure 1: Proposed role of microbiota in autoimmune diseases.

These data illustrate the dysbiosis role in triggering autoimmunity. Genetic susceptibility combined with increased intestinal permeability and dysbiosis, appear to increase the propensity of antigen-presenting cells to become activated and present antigen to cognate T cells, in secondary lymphoid organs, leading to the development of autoreactive lymphocytes [15]. Autoimmunity typically wanes over time [16]. Thus, it is appealing to speculate that relapses could be linked to the intricate relations where microbiota interrelates. Generally, a diverse microbiota is a sign of intestinal health. Restricted diversity emerges as a mark of a variety of disease states including autoimmunity [17,18]. Interestingly, a dysbiosis characteristic signature was found in patients with Behçet disease [19].

The Microbiota and Ocular Disease

Most models of autoimmune uveitis require inoculation with some retinal antigen in adjuvant to trigger disease. Horai et al. [20] developed a mouse model of spontaneous uveitis in that activation of retina-specific T cells was dependent on intestinal commensal microbiota, hypothesizing, that activation of autoreactive T cell receptors by commensal microbes could be a common trigger of uveitis, enlightening the paradox of how spontaneous autoimmunity can occur in an immune privileged site. In a model of experimental autoimmune uveitis, Nakamura et al. [21] suggested a protective and, equally, potentially pro-uveitogenic, intestinal microbiota.

In this study, the severity of the uveitis was modulated with oral antibiotics raising the idea of using a short course of antibiotics followed by repopulation of the intestine with beneficial species to mitigate disease severity.

Ocular Surface Microbiota

Most of the studies evaluating ocular surface microbiota have been performed with older technology that could not access for accurate biodiversity. However, more recent studies with NGS technology, found that healthy ocular surface microbiota is paucibacterial when compared to adjacent skin and different mucosa [22]. Greater bacterial counts are present in contact lens wear and dry eye disease [23-24].

Conclusion

There is increasing evidence that the microbiota has potent immunoregulatory functions, consequently, investigation with respect to ocular inflammatory diseases is wide open and auspicious.

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