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Review

Microbiota at the crossroads of autoimmunity

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ABSTRACT

Autoimmune diseases have a multifactorial etiology including genetic and environmental factors. Recently, there has been increased appreciation of the critical involvement of the microbiota in the pathogenesis of autoimmunity, although in many cases, the cause and the consequence are not easy to distinguish. Here, we suggest that many of the known cues affecting the function of the immune system, such as genetics, gender, pregnancy and diet, which are consequently involved in autoimmunity, exert their effects by influencing, at least in part, the microbiota composition and activity. This, in turn, modulates the immune response in a way that increases the risk for autoimmunity in predisposed individuals. We further discuss current microbiota-based therapies.

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1. Introduction

The incidence of autoimmune diseases is estimated at 3–5% worldwide [1]. Autoimmunity is known to have a genetic component [2,3];

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however, concordance rates of autoimmune diseases in monozygotic twins are incomplete, ranging between 12 and 67% [2], indicating a multifactorial etiology. In addition, the differences in autoimmunity incidence rates in different ethnic groups and geographical locations suggest the involvement of environmental factors. Lifestyle, exposure to infection, and nutrition, were all previously implicated [4]. Recently, the critical involvement of microbiota in health, as well as in many diseases including autoimmunity, is gaining attention [4]. Accumulating evidence suggests that the microbiota can be affected by both the environment and genetics, while subsequently influencing the human body with critical implications to our wellbeing [4].

The human microbiome is the genomic collection of the entire repertoire of human-associated microorganisms, the microbiota. Our microbiota account for 1–2 kg of our body weight, and is estimated to outnumber our own cells by an order of magnitude, and our genetic content by two orders of magnitude [4]. The largest microbial community is found in the gut, especially in the large colon where 100 trillion microbes reside [4]. On a day-to-day basis, this symbiosis is beneficial in activities including digestion of nutrients, xenobiotic degradation, vitamin production, and protection from pathogens [4].

At times, homeostasis is disturbed, and changes in microbial composition and diversity occur; these shifts are termed dysbiosis. Dysbiosis, especially in the gut, has been linked in recent years with disease states, but a direct causal relationship cannot be determined in every case. One of the first examples linking microbiome composition and disease occurs in obesity, in which an increased ratio of members of the Firmicutes phylum versus members of the Bacteroidetes was observed in both humans and mice. Moreover, in fecal microbiota transplantation (FMT) to germ free (GF) mice (raised under sterile conditions), the mice receiving the "obese" gut microbiota gained more body fat than mice administered microbiota derived from lean gut [5,6]. Besides obesity, changes in microbiota profiles have also been linked to a growing list of diseases such as metabolic syndrome [7], diabetes [8] and malignancy [9]. This connection was also demonstrated in autoimmune diseases, including systemic lupus erythematosus (SLE) [10], rheumatoid arthritis (RA) [11], inflammatory bowel disease (IBD) [12], psoriasis [13], multiple sclerosis (MS) [14], celiac disease [15], and Bechet's disease [16].

In this review, we describe evidence connecting microbiome dysbiosis with autoimmunity; we discuss the potential indirect effects of genetic and environmental factors on autoimmune pathogenesis through their effects on microbiota composition and activity.

2. Methodology of microbiome analysis

Our understanding of the microbiome has increased tremendously due to a series of technical advances. Culture-based methods support growth of less than 1% of the entire microbial communities under laboratory conditions, whereas next generation sequencing (NGS) techniques allow characterization of entire bacterial communities without requiring any growth in culture. This process classifies bacterial members based on sequencing of conserved regions of the versatile bacterial 16S rRNA gene, amplifying them using universal bacterial primers (Fig. 1), followed by sequencing and bioinformatic analysis to identify the species present and their relative abundance. Whole genome shotgun sequence analysis further facilitates the identification of microbial genes, and metatranscriptomics provides an understanding of some of the functions carried out by these communities [17]. These techniques are complemented by two relatively new methods, metabolomics and metaproteomics, which identify the metabolites and proteins of the microbiome, respectively (Fig. 1).

These advances in technology have enabled the characterization of the composition of the healthy microbiome, and identification of alterations in disease states. The two major sequencing efforts are concentrated at the National Institutes of Health (NIH) Human microbiome project [18], and The Metahit project [19]. However, with the increased recognition of the numerous factors influencing microbial composition including geography, diet, and age, recent years have witnessed more defined sequencing projects dissecting distinct populations; these include The American Gut, The British Gut, and Eldermet (the elderly microbiota) [20]. Although the microbiome also contains viruses, Archaea, and Eukaryotes, we focus here specifically on the bacterial component.

3. Microbiota composition and autoimmune diseases

The immune system, which co-evolved with the microbiota, has a complex challenge, on one hand inducing and maintaining tolerance to indigenous bacteria, while on the other hand, being able to initiate an effective immune response against potential insults from commensals, pathobionts (normally symbiotic, but pathogenic in the context of dysbiosis), and external pathogens when crossing the epithelial barriers [21,22].

While the function of the immune system impacts microbial inhabitation and activity, as indicated by models in which the activity of the immune system is compromised (see below) [23–26], the microbiota, in turn, modulates the development and tunes the function of innate and adaptive immunity, as demonstrated in models including germ free (GF) mice [27–29]. For example, presence of the microbiota is required for the expression of nucleotide-binding oligomerization domain 2 (NOD2) [30] and activity of NLRP6 [31], both associated with the innate arm of the immune system, necessary for bacterial recognition. The presence of microbiota also affects adaptive immunity, including peripheral differentiation of T helper (Th) cells, especially of T regulatory (Treg) and T helper 17 (Th17) cells [32]; certain *Clostridia* species are associated with increased numbers of Treg cells in the mouse colon [33], while segmented filamentous bacteria (SFB) promote the development of Th17 cells in mice [34]. Some of the mechanisms by which the bacteria shape the functions of the immune system are starting to be revealed, and include the following findings [35]: (i) metabolic products generated from dietary substrates such as short chain fatty acids (SCFAs), continuously regulate the innate and adaptive immune function; for example, butyrate regulates macrophage function, and induces differentiation of Treg cells [36,37]. (ii) Some bacterial metabolites have an immunomodulatory effect; the product of several strains of *Bacteroides fragilis* (*B. fragilis*), the zwitterionic polysaccharide A (PSA), has anti-inflammatory activities, acting through the Toll-like receptor (TLR) 2. (iii) Microbiota-modulated host metabolites can impact the activity of immune proteins; for example, the microbial-modulated-bile acid component activates the NLR6 [31]. When the homeostasis-maintaining dialog between the microbiota and the immune system is harmed, as a consequence of external or internal cue-induced dysbiosis or immune dysfunction, uncontrolled inflammatory conditions or breakage of the delicate tolerance towards microbiota can initiate or promote autoimmunity. There is increasing evidence for the key role of the gut, oral and skin microbiota in the pathogenesis of systemic and organ-specific autoimmune diseases, as we will describe below.

3.1. Gut microbiota

The adult gut is home to more than 1000 bacterial species [38] belonging to the four major phyla, Firmicutes, Bacteroidetes, Proteobacteria and Actinobacteria, and additional phyla such as Cyanobacteria, Fusobacteria and Verrucomicrobia [39]. Despite the fact that the fecal microbiome is often chosen as a representative sample of the gastrointestinal microbiome, we know today that the microbiome varies quite dramatically along the gastrointestinal (GI) tract (stomach, small intestine and large intestine). The stomach, which is the most acidic part of the GI tract, was believed for a long time to be germ free, until the discovery of *Helicobacter pylori* changed this paradigm [40]. Today, we are aware of the existence of a stomach microbiota (with the lowest microbial biomass in the GI tract) including members of all four major phyla, with *Streptococcus* being the predominant genus, and the other characteristic genera including