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REVIEW

The gut microbiome in autoimmunity: Sex matters

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Abstract Autoimmune diseases like rheumatoid arthritis are multifactorial in nature, requiring both genetic and environmental factors for onset. Increased predisposition of females to a wide range of autoimmune diseases points to a gender bias in the multifactorial etiology of these disorders. However, the existing evidence to date has not provided any conclusive mechanism of gender-bias beyond the role of hormones and sex chromosomes. The gut microbiome, which impacts the innate and adaptive branches of immunity, not only influences the development of autoimmune disorders but may interact with sex-hormones to modulate disease progression and sex-bias. Here, we review the current information on gender bias in autoimmunity and discuss the potential of microbiome-derived biomarkers to help unravel the complex interplay between genes, environment and hormones in rheumatoid arthritis.

Contents

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1. Introduction

Autoimmune diseases are characterized by alterations in normal immune function, resulting in hyperactive immune response against self proteins and tissues. Even though the etiology of autoimmune disorders is unknown, extensive clinical research over the past decade has pointed to genetic and environmental factors that interact to trigger disease. The genetic basis of autoimmunity is associated with a complex array of risk loci, the most important being those located in the Major Histocompatibility Complex (MHC), conferring susceptibility or resistance to disease [1]. Different disease outcomes in genetically identical individuals [2] imply that environmental triggers such as diet [3], infections and smoking exacerbate autoimmunity [4–6]. Although, in these studies, environment-derived antigens have been reported to increase (inflammatory reactions), mechanistic insight into how autoimmunity arises remains largely obscure.

Recent advances in "omic"-based approaches (metagenomics, metabolomics and proteomics) and bioinformatics have facilitated our understanding of the mechanisms of a broad range of diseases and have allowed us to identify potential biomarkers for diagnosis and therapeutic intervention [7]. One particular area of research receiving increasing attention over the past 5 years has focused on using omic-based techniques to study how the gut microbiome, the collection of bacteria, viruses, fungi and protozoa lining the gastrointestinal mucosa, significantly impacts health and disease [8–10]. These vastly diverse microbial communities not only play a vital role in nutrient synthesis and energy harvest from foods but also tightly regulate the innate and adaptive branches of immunity [11–16]. Recent research about the role of gut microbes in adaptive immune response has substantially changed our understanding of how genes, environmental factors and our "second genome" (the gut microbiome) interact to influence autoimmunity.

In this review we focus on the sex-bias of autoimmune disorders that, although well documented, still lacks mechanistic insight with regard to genetic and gut microbial interactions. Studies in humans and mouse models have revealed that females are 2–10 times more susceptible than males into a wide range of autoimmune disorders, including rheumatoid arthritis (RA), Multiple Sclerosis (MS), systemic lupus erythematosus (SLE), myasthenia gravis (MG), Sjogren's syndrome and Hashimoto's thyroiditis [17,18]. Yet, recent evidence is just beginning to emerge linking sex-specific microbial clades during disease progression, and pointing to complex interactions between gut microbes, genetic factors, environment and sex hormones. This review does not intend to discuss the current knowledge on the genetic or environmental triggers of autoimmune disorders and gender-bias, which have been elegantly reviewed elsewhere [19–22]. Here, we review the current literature relating gut microbes to the sex-based differences observed in various autoimmune disorders and discuss how diverse experimental platforms contribute to developing useful biomarkers for disease progression and for therapeutics.

2. The gut microbiome and autoimmunity

Mucosal surfaces are exposed daily to various environmental factors and therefore require an effective protection that can efficiently eliminate the majority of external agents. The mucosa-associated lymphoid system (MALT), which carries most of the immunologically active cells in the body, is the main barrier against potential insults from gut commensals and external agents. A characteristic feature of mucosal immunity that distinguishes it from systemic immunity is the maintenance of tolerance to non-dangerous antigens in the gut [23–26]. Intestinal bacteria are necessary for the development of competent mucosal immunity. Experiments with germ-free (GF) and specific-pathogen free mice (SPF) have shown that stimuli from intestinal commensals are required for maturation, development and function of important components of humoral and cell-mediated immunity [27,28]. Bacterial metabolites and metabolic products generated from specific dietary substrates, mainly short chain fatty acids (SCFA), also regulate immune function. For instance butyrate is reported to exert immunomodulatory effects on intestinal macrophages and induce differentiation of T regulatory cells resulting in inhibition of IFN-γ-mediated inflammation [29,30]. Thus, a homeostatic environment between the host and microbes is maintained by keeping these microorganisms from crossing the intestinal mucosa, yet maintaining tolerance to exploit the beneficial contribution of microbes to host physiology. However, failures in the epithelial integrity and mucosal immunity allow for bacteria to cross this barrier, triggering a pro-inflammatory response systemically. Consequently, diet–host–microbe molecular interactions are critical components of immune-competence as well as autoimmune disease development.

A growing body of evidence has linked specific signatures of microbial clades to various autoimmune diseases. Additionally, there is a strong association between sex and incidence of disease in a variety of conditions. Thus, a deeper understanding of the gut microbial composition in males and females will be informative for sex-based treatment options. Although very few studies have made an association with the sex-biased nature of diseases, type I diabetes (T1D), an autoimmune disease occurring with male to female ratio of 3:2 in populations of European descent aged 15–40 years [31], is perhaps the most studied disorder for correlations with the gut microbiome. Patients with T1D have shown shifts in ratios of the main phyla within the gut microbiome exhibiting decreased Bacteroidetes:Firmicutes ratios, lower abundance of potential butyrate producers, and lower bacterial diversity [32]. A recent study in children showed that low abundance of bacteria typically associated to lactate and butyrate production was associated with β cell autoimmunity [33]. Additional evidence comes from another study where T1D incidence was associated with an increased abundance of specific taxa such as *Clostridium* and decreased *Bifidobacterium* and *Lactobacillus* compared to healthy subjects [34]. NOD mice develop disease with an increased incidence in SPF compared to GF conditions suggesting a potentially protective role of the gut commensals [35]. This is supported by the observations where segmented filamentous bacteria (SFB) were shown to segregate with protection from diabetes in NOD female mice [36]. Although the mechanism of the gender-bias protection is yet to be elucidated, it can, in part, be explained by an increase in testosterone levels by SFB [37]. Exploratory analyses in female-biased MS showed a decrease