



Review

The possible role of oral microbiome in autoimmunity



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ABSTRACT

Objective: The human microbiome refers to the entire habitat, including microorganisms, their genomes and the surrounding environmental conditions of the microbial ecosystem. When the equilibrium between microbial habitats and host is disturbed, dysbiosis is caused. The oral microbiome (OMB) has been implicated in the manifestation of many intra- and extraoral diseases. Lately, there has been an intense effort to investigate and specify the relationship between microbial complexes, especially that of the oral cavity and intestine and autoimmunity. This study aimed to review the current literature about the possible role of the OMB in the pathogenesis of autoimmune diseases.

Methods: We searched for published articles in English indexed in PubMed, Medline, Research Gate and Google Scholar using a search strategy that included terms for oral microbiome, autoimmune diseases, dysbiosis and next-generation sequencing.

Results: An important number of articles were gathered and used for the description of the possible impact of dysbiosis of OMB in the pathogenesis of Sjögren's syndrome, systemic lupus erythematosus, rheumatoid arthritis, Behcet's disease, Crohn's disease and psoriasis.

Conclusion: This review article draws attention to the relationship between OMB and the triggering of a number of autoimmune diseases. Although this specific topic has been previously reviewed, herein, the authors review recent literature regarding the full list of nosological entities related to the OMB, point out the interaction between the microbiome and sex hormones with regard to their role in autoimmunity and discuss novel and promising therapeutic approaches for systemic autoimmune diseases. Furthermore, the question arises of whether the OMB is associated with oral bullous autoimmune diseases.

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Introduction

Defining the human microbiome

The term “microbial flora” refers to the entirety of the microorganisms that exist in the human body, including opportunistic, commensal and pathogenic. This term refers to the population of microorganisms that inhabit the skin surface and its deeper layers, saliva, oral mucosa, upper respiratory tract, gastrointestinal and urogenital tracts and the conjunctiva. Each of these human body sites has its own unique microbial flora (Davis, 1996; Dong et al., 2011; Grice et al., 2009; Ley et al., 2006; Martin, 2012). The term “microbiome” is used to describe the entire habitat, including the microorganisms, their genomes and the surrounding environmental conditions of the respective complex microbial ecosystem (Turnbaugh et al., 2007). The concept of the human microbiome was first suggested by Lederberg and McCray (2001), who coined the term “microbiome” to emphasize the significance of human body colonization by host microorganisms in both healthy and diseased individuals.

The human microbial flora, principally that of the gut, is estimated to consist of 10 to 100 trillion commensal microorganisms (Ursell et al., 2012). Only 10% of the cells detected in the human body actually have human origin. The overwhelming majority, 90%, is part of the microbial flora (Ley et al., 2006). The oral cavity offers an ideal environment for the colonization and growth of microorganisms because it provides warmth, humidity and nutritional abundance. This results in hundreds of microorganisms, including viruses, protozoa, fungi, archaea and bacteria, that constitute the oral microbiome (OMB), making it the second most complex microbiome in the human body (Dewhirst et al., 2010; Human Microbiome Project, 2012). Nearly 1000 species of bacteria can be detected in the oral cavity. Specifically, >750 species of bacteria have been identified with culture-independent methods and >250 species have been isolated, cultured and characterized (Paster et al., 2006). Saliva, oral mucosa and tooth surfaces are the three available sites in the human mouth for microbial colonization, leading to the formation of respective microbiomes. The composition of the microbiome displays significant diversity in different oral sites, even in neighboring ones such as the subgingival and supragingival dental plaque and the dorsal or lateral surface of the tongue (Ahn et al., 2012). These differences are probably due to variants of intrinsic and extrinsic factors, such as stress and smoking, respectively (Pozhitkov et al., 2011).

Dysbiosis

Commensal microorganisms play a central role in maintaining homeostasis and health, not only by blocking microbial activity but also by reinforcing the human immune system through specialized mechanisms (Kau et al., 2011). The dynamic interaction between these microorganisms and the organism is both continuous and balanced and it is performed to such a degree that the host human organism could be described as a superorganism

(Goodacre, 2007). However, the influence of various external factors could lead to microbial imbalance on or inside the body, causing so-called dysbiosis. In this situation, the microbial colonies involved lose their ability to control each other's population development, which results in the gradual prevalence of one or more colonies and can have a pathogenic effect on the organism (Tamboli et al., 2004). Furthermore, whereas under normal conditions of equilibrium, the organism (through waste disposal mechanisms) can easily dispose of the bioproducts of microbial colonies, in cases of an imbalanced dramatic development of microbial colonies, the large amount of microbial waste can negatively affect the human organism, which can no longer easily dispose of these products (Carding et al., 2015). Some factors implicated in dysbiosis include the genotype of the host, a Western way of life, nutrition, irrational use of antibiotics in medicine and agriculture, excessive adherence to hygiene rules and alcohol abuse (Spor et al., 2011). This phenomenon takes place most often in the intestinal microbiome as well as in the OMB, causing a number of diseases (Karczewski et al., 2014).

A dysbiotic shift of oral host microorganisms triggers disease entities, such as dental caries, periodontal diseases, peri-implant inflammation and halitosis (Pozhitkov et al., 2011; Wade, 2013). There are oral bacteria that prevent pathogenic colonization (colonization resistance). When these bacteria are eliminated, a serious possibility exists of triggering opportunistic infections. Also, the antagonistic or synergistic interaction between commensal-pathogenic microorganisms is widely accepted to be more likely to be implicated in eliciting oral diseases than the presence or absence of particular bacterial species (He et al., 2015). Furthermore, unlike other infections, the induction of many oral diseases requires the combined effect of more than one etiological agent of infection (Alcaraz et al., 2012).

Aside from the aforementioned oral diseases, studies have investigated the link between the OMB and systemic and distant diseases. In some cases, the OMB was evaluated as playing a possible etiological role in certain systemic disease, whereas in others it was thought to be the result (Table 1).

Microbiome and autoimmunity

Recent epidemiologic and clinical reports have described a dramatic increase in the incidence of several autoimmune and inflammatory diseases in the developed world. Although the aforementioned diseases exhibit a strong genetic component, the rapidity of the increase cannot be explained solely by genetic drift. Accumulating research evidence suggests that this instead might be the result of host-microorganism equilibrium disturbance (Macia et al., 2012; Myasoedova et al., 2010). Environment, including microorganisms, plays a major role in shaping the immune system and accounts for the heterogeneity of immunologic parameters among individuals. The fact that autoimmune diseases affect some people and not others is partly based on this heterogeneity (Brodin et al., 2015).

Table 1
Link between OMB and systemic diseases.

Nosological entity	Links to OMB
Tumor	OMB is similar among patients with oral squamous cell carcinoma and different from that of healthy individuals (Macia et al., 2012) High levels of <i>S. mitis</i> and <i>N. elongata</i> in the salivary microbiome of patients with malignancy of the pancreas (Farrell et al., 2012)
Cardiovascular diseases	Oral bacteria can cause infective endocarditis (Mylonakis and Calderwood, 2001) Oral bacteria <i>Streptococcus Veillonella</i> , <i>Porphyromonas gingivalis</i> , <i>Fusobacterium nucleatum</i> , <i>Tannerella forsythia</i> and <i>Neisseria</i> detected in atherosclerotic plaques. <i>Fusobacterium</i> , <i>Streptococcus</i> and <i>Neisseria</i> levels were related to plasma cholesterol levels (Koren et al., 2011). Oral bacteria found in abscesses (Marques da Silva et al., 2004; Schiff et al., 2003)
Cerebral or hepatic abscesses	
Cystic fibrosis	Oral bacteria identified in lungs of patients with cystic fibrosis (Rogers et al., 2006)
Miscarriage or low-weight infant	Oral bacteria identified in the uterus of women who miscarried or had preterm birth (Mitchell-Lewis et al., 2001)
Obesity	Higher levels of <i>Selenomonas noxia</i> found in the saliva of overweight women (Goodson et al., 2009)

OMB, oral microbiome.

Until recently, the prevailing theory of autoimmunity proposed that the body attacks the self, which was considered to be sterile. However, recent research has shifted its focus to studying the connection between autoimmunity and microbes (Proal et al., 2013). Consequently, dysbiosis is not only a biomarker of inflammatory diseases, but also the initiator of autoimmune reactions (Honda and Littman, 2012).

Advanced technologies for microbiome analysis have contributed over recent years to the establishment of its involvement in several autoimmune diseases, such as rheumatoid arthritis (RA), Type 1 diabetes, ankylosing spondylarthritis, psoriasis, psoriatic arthritis, systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), Crohn's disease (CD), Behcet disease (BD), multiple sclerosis, giant cell arteritis and Kawasaki disease (Coit and Sawalha, 2016).

The microbiome influences the host immune system through various factors and mechanisms. The constitutive stimulation of Toll-like receptors, pathogen persistence, molecular mimicry and epitope spreading are some of these mechanisms. Microbes can also cause epigenetic changes that include changes in gene function through DNA methylation, posttranslational histone modification and micro-RNA alteration without changes in DNA sequence (Nikitakis et al., 2017).

Oral microbiome and autoimmune diseases

Sjögren's syndrome

SS is a systemic chronic autoimmune disease, characterized by B-cell hyperactivity, which produces antibodies and by lymphocytic infiltration of the exocrine glands resulting in their destruction. Salivary and lacrimal glands are primarily attacked, leading to a significant reduction in saliva and tear production, which subsequently leads to the two most prominent symptoms of the disease: oral and ocular dryness, respectively. The disease occurs nine times more often in women than in men, with a peak of occurrence in the menopausal age group. SS is divided into primary and secondary forms, with the secondary occurring along with other autoimmune diseases, such as SLE or RA (Mavragani and Moutsopoulos, 2014).

Hyposalivation in patients with SS has been associated with an increased number of species of the genus *Candida*, as well as an increase in the number of *S. mutans*, species of the genus *Lactobacillus* (e.g., *Lactobacillus* spp on tooth surfaces). This is clinically relevant because reduced salivary secretion, which serves a protective function for the oral cavity, predisposes to the development of caries (typically cervical) and oral candidiasis (Almstahl et al., 2003; Shinozaki et al., 2012).

However, a study using high throughput sequencing of 16S rRNA revealed a shift in OMB in patients with SS who had normal

salivation flow compared with healthy controls. On the phylum level, Firmicutes had a significantly higher frequency in patients, but Synergistetes and Spirochaetes were significantly depleted in SS. On the genus level, *Streptococcus* and *Veillonella* displayed about a two-fold increase in patients with SS. Finally, on the species level, the *Veillonella atypica* and *Veillonella parvula* groups dominated in patients, whereas *Prevotella melaninogenica* was the major species in controls. In general, the microbiome demonstrated a lower diversity and richness in patients, where a depletion of nearly 17% in the number of genera was detected. This study showed that dysbiosis of the OMB is a key characteristic of SS and can occur independently of hyposalivation (Siddiqui et al., 2016).

In most studies that analyzed the composition of the OMB in patients with SS, researchers included patients with SS who had dry mouth, controls with dry mouth without SS and healthy controls. Rusthen et al. (2019) used 16S rRNA gene sequencing to analyze the saliva microbiome in patients with SS, non-SS sicca patients and healthy controls. The total result of the study indicated a significantly different microbiome composition in patients with SS compared with the non-SS group and healthy controls, pointing out that hyposalivation is not the only reason for microbiome diversity in SS.

Li et al. (2016) analyzed buccal mucosa microflora using high throughput sequencing and found a relative abundance of *Proteobacteria* in the SS group, specifically of the genus *Ralstonia* and a lower diversity of microbiome composition in patients with primary SS compared with healthy individuals. De Paiva et al. (2016) examined the microbiome of the tongue in patients with primary SS, who were found to have a decrease in *Leptotrichia* and *Fusobacterium* and an increase in *Streptococcus* species. On the other hand, van der Meulen et al. (2018) used 16S rRNA sequencing and suggested that dysbiosis of the buccal mucosa microbiome in patients with SS resembles that of controls who had dry mouth but no SS.

Szymula et al. (2014) are the only researchers who have studied the role of bacteria in SS development. They found that a microbial protein (von Willebrand factor type A) that carries the peptide Ro60 and is present in the commensal oral bacteria *Capnocytophaga ochracea* could activate T cells with a receptor for Ro60 (SSA) through dendritic cells. SSA autoantibodies might be produced when the activated Ro60-reactive T cells in turn activate B cells to become plasma cells. If next-generation sequencing (NGS) methods for analyzing the OMB in patients with SS reveal an increased relative abundance of *C. ochracea* in the oral cavity, then the microbiome–SS connection could be explained by the molecular mimicry theory whereby immune cells react with self-antigens, which share epitopes with foreign antigens produced by microorganisms (Cusick et al., 2012).

Rheumatoid arthritis

RA is a chronic systemic disease of the synovial joints and is characterized by inflammation, hyperplasia and the production of autoantibodies, such as the rheumatoid factor and anticitrullinated protein antibodies (ACPAs). The result is symmetric polyarthritis, characterized by the destruction of cartilage and bone (McInnes and Schett, 2011). Both genetic and environmental factors contribute to the pathogenesis of the disease. However, the low concordance rate of RA in monozygotic twins indicates that environmental factors play a major role in disease development (Sakkas et al., 2014).

The OMB may be considered as an environmental factor. There is substantial evidence to suggest that the periodontal pathogens *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis* are regarded as autoimmunity triggers for RA. Moreover, periodontium may be a triggering site. Patients with RA have been found to have a higher prevalence of periodontitis compared with healthy individuals (Fuggle et al., 2016). *A. actinomycetemcomitans* secretes leukotoxin A, which forms pores on the neutrophil membranes, leading to neutrophil hypercitrullination, which in turn results in the release of citrullinated autoantigens in the gums. Research has shown that 47% of patients with RA had a previous *A. actinomycetemcomitans* infection compared with 11% in controls (Konig et al., 2016).

P. gingivalis has also been found to lead to citrullinated autoantigens and ACPA production in two different ways: By way of peptidyl arginine deiminases, it can cleave proteins at arginine residues and citrullinate those residues to produce more autoantigens to which the host immune system is exposed and by neutrophil extracellular trap (NET) formation induced during the process of NETosis. ACPAs induce NETosis; this, in turn, provides citrullinated autoantigens (Guo et al., 2018; Socransky et al., 1998).

ACPA levels have been observed to be significantly higher in people with subgingival *P. gingivalis* and have a positive correlation with levels of antibodies against the specific bacterium, which have been found to be elevated in patients with RA (Mikuls et al., 2014). Conversely, a study of the subgingival plaque microbiome in patients with new onset and chronic RA as well as healthy controls showed no difference in composition. Also, species of *Prevotella* and *Lep-totrichia* were characteristic of patients with new-onset RA, regardless of periodontal disease severity. Finally, *P. gingivalis* was found in almost equal abundance in both patients with new-onset and chronic RA as well as healthy controls (Scher et al., 2012). Consequently, although based on research findings, the role of *P. gingivalis* in the pathogenesis of RA is still in question and periodontal treatment as an adjuvant for RA drug therapy significantly reduces the severity of the disease clinical course (Erciyas et al., 2013).

Apart from the relationship between periopathogens and RA, recent evidence draws attention to the changes and decreased diversity of the rest of the OMB as a key player in the etiopathogenesis of RA. The link between OMB and RA in animal models of arthritis has been established and is now receiving increasing attention in human studies (Drago et al., 2019). Zhang et al. (2015) examined the salivary and dental plaque metagenome of patients with RA and observed significant differences in the microbial composition in comparison with healthy controls. Patients with RA showed an abundance of *Veillonella* and anaerobic species, such as *Lactobacillus salivarius* and *Atopobium* species, whereas controls were enriched in *Haemophilus* species, aerobic species and *P. gingivalis*. Furthermore, the use of antirheumatic drugs increased the abundance of some underrepresented taxa in patients with RA compared with healthy controls, indicating possible participation of microbes in ameliorating the symptoms of the disease.

Behcet's disease

BD is a rare multisystemic, autoinflammatory, immune-mediated vasculitis that causes blood vessel inflammation. Originally, BD was seen along the Silk Road, but due to immigration, the disease is now found worldwide. BD may manifest with a triple-symptom complex of recurrent oral aphthous ulcerations, genital ulcers and uveitis. Oral aphthous represents the initial clinical sign of the disease in >80% of cases (Bulur and Onder, 2017). This high percentage of oral involvement leads to speculation that the oral environment may participate importantly in the etiopathogenesis of the disease, which remains unclear to date.

Bacterial involvement has long been suggested as a potential etiologic factor for BD. Studies concerning cutaneous and conjunctival microbiota and the serum of patients with BD previously indicated an association between some streptococcal species and BD (Lehner et al., 1991; Narikawa et al., 1995; Yokota et al., 1995). In more recent studies, the administration of antibiotics or probiotics had an impact either on the duration and extent or the frequency of clinical signs and symptoms of BD (Alpsoy, 2012; Consolandi et al., 2015).

Seoudi et al. (2015) were the first to examine the salivary and oral mucosal microbiota from ulcer sites of patients with BD. They compared the results with those of nonulcer sites in the same patient, healthy controls and recurrent aphthous ulcers. They found increased colonization with *Rothia dentocariosa* of the nonulcer sites of BS, high colonization with *Streptococcus salivarius* of ulcer sites compared with recurrent aphthous ulcers and high colonization with *Streptococcus sanguinis* of ulcer sites compared with healthy controls. Moreover, they found depleted colonization with *Neisseria* and *Veillonella* of ulcer and nonulcer sites compared with healthy controls. The salivary microbiota of patients with active BS was significantly colonized with *Bifidobacterium dentium*, *Prevotella histicola* and *Candida albicans* and less frequently colonized with *Campylobacter concisus*, *Clostridiales* spp., *Fusobacterium periodonticum*, *Gemella sanguinis*, *Neisseria* spp. and *Oribacterium sinus* compared with that of healthy controls.

In another study, Coit et al. (2016) investigated the salivary microbiome in patients with BD using high-throughput sequencing of the 16S rRNA V4 region and compared the results with those of healthy controls and saliva samples from patients with BD after dental and periodontal treatment. The microbial community structure had a significantly decreased diversity compared with that of the controls, with *Haemophilus parainfluenzae* and *Alloprevotella* showing an overabundance. For the subset of patients who had root scaling and dental care, there was no significant change in the diversity of salivary microbiota.

Crohn's disease

CD is a type of chronic inflammatory bowel disease, along with ulcerative colitis (UC). It is characterized by the development of granulomatous inflammation at any part of the gastrointestinal tract from the mouth to the anus but most commonly affects the colon and terminal ileum. CD can occur at any age, with a peak incidence during the second and third decade of life. In the United States, the prevalence is estimated at 58 per 100,000 children and 119–241 per 100,000 adults and is increasing for both groups (Veauthier and Hornecker, 2018). Clinical signs and symptoms depend on the location of the lesions. Oral manifestations appear in a percentage ranging from 0.5% to 50% and are more common in men and children. Manifestations can include a wide variety of lesions, from nonspecific minor aphthous lesions, mucogingivitis and angular cheilitis to more specific lesions, such as cobble-stone mucosal appearance, mucosal tags, pyostomatitis vegetans, deep linear ulcerations and swelling of the face (mainly lips) known as

orofacial granulomatosis (Muhvić-Urek et al., 2016). The pathogenesis of CD is currently thought to be the result of an intense inflammatory response to the commensal gut microbiome in genetically susceptible individuals. Data from studies concerning the OMB are few and scarce (Lucas López et al., 2017).

Docktor et al. (2012) examined tongue and buccal brushings from patients with CD and UC as well as healthy controls. The researchers presented evidence to suggest that the OMB is uniquely altered in patients with CD. They mainly demonstrated a marked decrease in overall microbial diversity in CD. Furthermore, a significant reduction of the levels of *Fusobacteria* and *Firmicutes* and an increase in the level of *Bacteroidetes* was noted in tongue samples of patients with CD compared with those from patients with UC or healthy subjects.

Said et al. (2014) studied the composition of salivary microbiota of patients with CD and UC as well as healthy controls. They demonstrated a significant decrease in *Proteobacteria* with a simultaneous increase in *Bacteroidetes*. The genera *Streptococcus*, *Prevotella*, *Neisseria*, *Haemophilus*, *Veillonella* and *Gemella* strongly contributed to dysbiosis of the salivary microbiota of patients. Moreover, analysis of immunological biomarkers of the saliva of patients concluded that the observed dysbiosis was associated with elevated inflammatory response of several cytokines with depleted lysozyme, some of which showed a powerful correlation with certain relatively abundant bacterial species.

Systemic lupus erythematosus

SLE is a multisystemic autoimmune disease that affects a number of organs, including the skin, joints, blood vessels, heart, kidneys and lungs. SLE primarily affects women of reproductive age. It is characterized by great diversity and heterogeneity in terms of clinical picture and course (Golder and Hoi, 2017). Oral manifestations are common and may occur in >40% of cases (Menzies et al., 2018). Distinctive self-antigens attacked by antibodies include nuclear peptides, nucleosomes, double-stranded DNA and Ro peptide (known as SSA), which is considered to be directly related to SS (Goldblatt and O'Neill, 2013).

Many studies have been conducted to explore the role of intestinal microbiome in the pathogenesis of SLE (Luo et al., 2017; Mu et al., 2017). However, the potential participation of the OMB in the disease still remains elusive. Corrêa et al. (2017) studied the microbial composition of subgingival dental plaque in patients with SLE by using 16S rRNA sequencing. The researchers found *P. nigrescens* to be correlated with higher values of the SLE severity index, *P. denticola* to be correlated with increased neutrophil levels and *P. melaninogenica* to be correlated with increased serum C-reactive protein levels in patients with SLE. Fabbri et al. (2014) evaluated the impact of periodontitis treatment on disease activity of SLE in patients under immunosuppressive therapy and found that controlling periodontal inflammation seems to abbreviate the immunosuppressive therapeutic response, supporting the hypothesis that periodontitis may be an important factor in the maintenance of the inflammatory response in SLE. On the contrary, De Araújo Navas et al. (2012) examined oral rinse samples from patients with SLE and healthy controls to evaluate the presence of *Staphylococcus* spp., *Enterobacteria* and *Pseudomonas* spp. and concluded that there is no difference in the frequency and microorganism levels between the two groups.

The frequent involvement of the oral mucosa in the clinical manifestation of the disease indicates that the local oral microenvironment may participate in the development of SLE or contribute to systemic involvement through the production of circulating autoantibodies against oral microbial products (Nikitakis et al., 2017). However, there is a need for further investigation to extract safe data on the disease.

Psoriasis

Psoriasis is a chronic, immune-mediated, inflammatory, multi-system disease with a prevalence of approximately 2% of the Western population. The disease can appear at any age but usually displays a peak incidence between 15 and 30 years of age and a later peak incidence between 50 and 60 years of age (Gudjonsson and Elder, 2007). Psoriasis predominantly affects the skin and joints, but the prevalence of oral manifestations differs among studies, with a prevalence of fissured tongue ranging from 9.8% to 47.5% and of geographic tongue between 5.6% and 18.1% (Picciani et al., 2016). Several risk factors are involved in its etiopathogenesis, including infections. The pathobiological mechanisms underlying psoriasis are not fully understood, but the driving factor appears to be an intense activation of the immune system (Kim et al., 2010).

Over the past few years, several cross-sectional studies have shown a 1.55-fold higher risk of periodontitis and increased periodontal disease activity in patients with psoriasis compared with healthy controls (Ungprasert et al., 2017). Even though the exact mechanism behind the increased risk is unknown, several possible explanations have been reported. One hypothesis refers to the common inflammatory mechanisms between psoriasis and periodontitis; an exaggerated immune response to the microbiota at the epithelial surfaces is observed in both diseases, which might suggest a shared genetic background that affects dendritic cells, T cells, keratinocytes and Toll-like receptor expression (Fernández et al., 2019; Kim and Krueger, 2015; Wilensky et al., 2014). Another hypothesis involves the activation of Th-17 cells and increased expression of interleukin 17, a protagonist in the pathogenesis of psoriasis, induced by bacteria involved in periodontal infection and their products (Blauvelt and Chiricozzi, 2018; Ohlrich et al., 2009).

Toward this direction, some rare cases report the regression of cutaneous psoriatic lesions after periodontal treatment (Akazawa et al., 2006; Murai et al., 2012). Periodontal infection control might be an attractive future therapeutic intervention for psoriasis.

Moreover, Belstrøm et al. (2020) studied stimulated saliva samples from patients with psoriasis, patients with periodontitis and controls without oral lesions by means of NGS of the 16S rRNA gene. They found that some bacterial taxa differentiated the salivary microbiota in patients with psoriasis from that of patients with periodontitis and orally healthy controls. This could mean that a distinct OMB contributes to the disease pathogenesis or, conversely, an impact of the disease itself on the composition of the OMB. Further investigation is required to clarify the relationship between psoriasis and OMB.

Microbiome and autoimmune bullous diseases

The category of immune bullous diseases includes entities characterized by the production of autoantibodies that target components of epithelial cells of the skin and mucosa (including oral mucosa), leading to destruction of epithelial bonding, which manifests clinically as the formation of blisters. These diseases comprise pemphigus, mucous membrane pemphigoid, bullous pemphigoid, linear immunoglobulin A bullous dermatosis and epidermolysis bullosa acquisita. In each of the diseases, different self-antigens are targeted by autoantibodies (Baum et al., 2014). Remarkable progress has been achieved regarding the identification of genetic risk factors for developing these diseases, but no environmental agent has been conclusively identified. Studies on the effect of the microbiome on disease inducement and manifestation are few and far between.

Miodovnik et al. (2017) compared the composition of the skin microbiome of patients with bullous pemphigoid and healthy individuals. The authors reported that the microbial phylum composition differs between the perilesional sites of patients with bullous pemphigoid and the same anatomic locations of healthy persons. In addition, the researchers reported the existence of a distinct cutaneous microbiome profile that correlated with bullous pemphigoid, which further strengthens the significance of commensal-host interaction on the immune mechanisms. Furthermore, the results of this research raise the possibility that the cutaneous microbiome may contribute to the pathogenesis of the disease.

Ellebrecht et al. (2016) observed that 20% of immunized mice with circulating autoantibodies of epidermolysis bullosa acquisita remained healthy. The immunization was conducted under identical genetic and environmental conditions. The mice that did not develop clinical disease showed a significantly higher richness and distinctly clustered diversity of the skin microbiome before immunization. This observation indicates that, regardless of the presence of circulating autoantibodies, the composition of the skin microbiome plays a significant role in the manifestation of the disease. The dominance of certain bacterial species appears to be protective against disease manifestation.

Techniques of microbiome study

The study of the human microbiome can be conducted by several means. Forty years ago, the establishment of Sanger sequencing was revolutionary because complete genome sequences could be decoded for the first time. This sequencing technique by synthesis served as a gold standard for genome analysis for a long time. Nevertheless, the need for less cost and time to process DNA segments, with larger throughput and less human resources, led to the gradual development and introduction of NGS technologies. These methods have constituted a breakthrough in DNA sequencing. They offer parallel, massive, deep sequencing of entire genomes at unprecedented speed and low cost. Hence, they represent the revolution in genomic research and have many clinical applications. Microbiology has gained a dramatic broadening of the spectrum of microbial genomes. There have been a number of sequencing platforms during the evolution of this technology belonging to either the first, second, or third generation of NGS (Vincent et al., 2017).

Interaction between microbiome and sex hormones

Women have a more intense immune response to foreign and self-antigens than men. This robust immune response leads to a higher tendency for women to develop autoimmune diseases, which might suggest a role of sex hormones in the pathogenesis of autoimmunity. Interestingly, 80% of autoimmune disease occurs in women. The strongest sex bias is observed in SS, SLE, autoimmune thyroid disease and scleroderma, where the ratio of women to men is 7:1 to 10:1. Disease severity and clinical course, response to therapy and overall survival rate may also differ between the two sexes (Ortona et al., 2016).

Sex hormones (estrogens androgens and progesterone) can connect to specific receptors on immune cells and contribute to the regulation of the development and function of the immune system (Klein and Flanagan, 2016). The exact molecular mechanisms of how female hormones regulate the innate and adaptive, humoral and cell-mediated immune responses are not yet fully elucidated, but studies have shown that they control homeostasis, gene expression and signaling processes in T and B lymphocytes to influence their function. Deregulation of these mechanisms may have

an impact on autoimmune disease. Androgens and progesterone are considered immunosuppressive and therefore play a protective role in autoimmunity, whereas estrogens are potent stimulators and therefore play a pathogenic role (Moulton, 2018).

Some studies indicate sex hormone-dependent microbiota composition in mice intestinal content in relation to age. Puberty appears to affect the male microbiota composition, which becomes less diverse than the female microbiota, which remains similar to the primary one of young mice. Importantly, a comparison of male, female and castrated male microbiota demonstrated that sex hormones rather than X chromosome-associated factors were important for the change in microbiota composition (Steegenga et al., 2014; Yurkovetskiy et al., 2013).

Moreover, a role of gut microbiota in the sex bias in autoimmunity has been revealed by different studies in animal models. Markle et al. (2013) demonstrated that early life microbial exposure alters sex hormone levels and contributes to the development of autoimmune disease in individuals with a high genetic risk. Under colonized settings, men and women either had distinct microbial communities that induced different hormonal responses or responded in a sex-specific manner to an identical community. The researchers showed that commensal colonization regulated testosterone serum levels and protected male mice from autoimmunity. Furthermore, the transfer of gut microbiota from adult males to immature females resulted in elevated testosterone levels, reduced inflammation and autoantibody production and robust protection against autoimmunity.

Thus, there appears to be a reciprocal interaction between microbiota and sex hormones to modify the risk of development and the course of the autoimmune disease progression. This interaction could explain the female predilection of the majority of autoimmune entities. OMB manipulations could provoke testosterone-dependent protection from these autoimmune diseases in a genetically high-risk individual.

Microbiome shift and therapeutic interventions

Conclusively targeting dysbiosis, which apparently contributes to the onset and progression of autoimmunity, could offer alternative therapeutic approaches for these diseases. Diet interventions, functional foods (e.g., probiotics and prebiotics) and fecal microbiota transplantation are some of the efforts that have been made to correct the malfunction of the disturbed microbiome in patients with SS, RA, SLE, BD and psoriasis to ameliorate disease severity and course (Chen et al., 2017; De Luca and Shoenfeld, 2019; Tasli et al., 2006). Given the crucial role of the OMB in a number of autoimmune diseases, altering its composition in favor of beneficial bacteria could offer a very promising future concerning the specific nosological entities. Future studies will be required to investigate the relationship between oral mammalian and commensals to develop novel immunomodulatory factors to suppress autoimmunity.

Conclusion

There are a growing number of studies concerning the role of the microbiome in immunity equilibrium loss. Substantial evidence connects gut dysbiosis to a significant number of autoimmune diseases and the OMB has been linked to some of these diseases, such as, SS, SLE, RA, BD, CD and psoriasis. Herein, summarized data show the impact of the OMB on those diseases. Identifying how dysbiosis of the OMB affects the onset and development of these diseases is the big challenge. To date, whether the observed changes of the microbiota result as a consequence of the disease process or a trigger to its onset remains enigmatic.

The evolution of molecular methods of microbiome analysis, such as NGS, can contribute remarkably to the in-depth investigation of the OMB down to the species level and can provide more accurate information for microbial changes in health and disease. Collectively, although an unambiguous role of the OMB in autoimmunity has been demonstrated in studies, the underlying detailed mechanisms are not entirely elucidated. In general, the OMB may influence the host immune system through Toll-like receptors, molecular mimicry, epitope spreading and antigen persistence.

Regarding the predisposition of women to the majority of autoimmune diseases, it is important to focus on the axis of microbiome-sex hormones-autoimmunity, where various interactions take place. Novel treatment approaches are currently under development to promote the growth of specific strains of beneficial bacteria. Prebiotics, probiotics and diet changes may constitute a very promising tool for modulating the OMB synthesis in favor of immunity protection.

With regard to bullous autoimmune diseases, it is clear that further research needs to be conducted to determine whether the microbe and even the OMB has any effect on autoimmunity. The authors are completing a new study on the role of the OMB on Pemphigus Vulgaris and thereby contributing to the large volume of data that emerges from the analysis of the human microbiome concerning disease status.

Conflicts of Interest

None.

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None.

Study Approval

The author(s) confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies.

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