Alternation of Microbiota in Autoimmune Disease

Minghui Yi*

Department of Molecular Biology and Biochemistry, University of California, California, United State

*Corresponding author: minghuy@uci.edu

Abstract. Immune system distinguishes self-antigens from non-self-antigen to protect the host from foreign threats. If losing this ability, the immune system can attack the host and lead to autoimmune diseases, which has high mortality although low prevalence. Microbiota closely interact with the immune system and functions to regulate the immune responses, thus are very likely to play a role in the autoimmune diseases. This paper discusses six autoimmune diseases, all of which are detected alternation of microbiota for the patients when comparing to that of the healthy controls. An imbalance between relative abundance of Bacteroidetes and Firmicutes can be a common characteristic of the patients. Probiotic treatments such as fecal microbiota transplantation (FMT) and probiotic supplements turn out to have an effect relieving the symptoms of autoimmune diseases. This suggests a great potential of probiotic treatment for the future development of better therapy for autoimmune diseases.

Keywords: Autoimmune diseases; Immune system; Microbiota; Fecal microbiota transplantation.

1. Introduction

Autoimmune diseases have an overall prevalence of 3-5% in the general population which is relatively uncommon, but the effects on mortality and morbidity is significant [1]. Over 80 types of autoimmune diseases affect different parts of the body. While the severity of symptoms is varied from one another, common symptoms of autoimmune diseases involve skin problems digestive problems as well as recurring pain and fever. The specific cause of autoimmune diseases is not clear, but some supposed risk factors are genetics, overweight, smoking and medication such as overuse of antibiotics [2]. The main treatments for autoimmune disorder are immunosuppressant drugs which suppress and regulate the overactivated immune systems, and anti-inflammatory drugs which relieve inflammatory and pain. While these treatments help to relieve symptoms of autoimmune diseases, they also have the side effect of weakening the normal immune function and increase the risk of infection. In fact, the microbiota can play an important role regulate the homeostasis of immune system. The microbiota is primarily composed bacteria, and some fungi, protozoa, and virus. Normally, the microbiota maintains a symbiotic relationship and contribute to the health of the host. It also dynamically interacts with the immune system, and thus closely associated with inflammation, immune tolerance, adaptive immunity, and autoimmune diseases [3]. Thus, treatments that alter and regulate the microbiota may have the potential to improve symptoms of autoimmune diseases. This paper discusses six autoimmune diseases regarding the comparison of the microbiota between patients and healthy samples, as well as some possible probiotic therapies for them.

The immune system is a complex system involving lymphoid organs, cells, humoral factors, and cytokines. It mainly functions to protect the host against pathogen infections and the intrusion of other foreign molecules. Based on the speed and specificity of the immune responses to antigens, immune system is divided into the two arms named innate immunity and adaptive immunity. Immune cells involve in innate immunity includes neutrophils, monocytes, macrophages, and the complement system. It is the first line of the immune system that provides immediate responses against pathogens and is not specific to single antigen. The adaptive immunity composes of T lymphocytes and B lymphocytes [4]. The adaptive immune system usually takes around one to two weeks to activates but can be antigen-specific with an enhanced immune response. While B cells can recognize and target specific antigens with the B cell receptors, T cells need to recognize specific antigen by matching the T cell receptor with the major histocompatibility complex (MHC) that presents antigen

proteins. It is essential for the immune system to distinguish foreign antigens from autoantigens and build up tolerance to the autoantigens. If the immune system mistakenly recognized autoantigen as foreign threat, the immune cells will infiltrate and attack the host cells thus result in autoimmune diseases.

2. Systemic lupus erythematosus (SLE)

Systemic Lupus Erythematosus (SLE) is a multisystemic autoimmune disease that can cause inflammation and permanent damage of organs in the long term. The disease has a lower incidence in children than in adults, and it is much more common in women with a woman to man ratio of 9:1. Also, the incidence and prevalence of SLE is vary in different geographic regions [5]. Besides the factor of gender, age and ethnicity, environment and diet may have impacts on SLE as well.

A comparison of gut microbiome profile of SLE patients to that of the healthy control samples indicates dysbiosis for SLE patients. The four bacterial phyla that dominate the human gut microbiome are Firmicutes, Bacteroidetes, Actinobacteria and Proteobacteria. Microbiota of SLE patients show a decrease in Firmicutes with an increase in Bacteroidetes. In addition, they have an increase in Rhodococcus, Eggerthella, Klebsiella, Prevotella, Eubacterium and Flavonifractor, and a decrease in Dialister and Pseudobutyrivibrio [6]. Most bacteroidetes bacteria release endotoxins and produce cytokine. In contrast, most firmicutes bacteria are anti-inflammatory [7]. As a result, a low Firmicutes/Bacteroidetes ratio in the gut microbiome can cause more inflammation and overactivation of the immune system, which contribute to autoimmune disorder.

One way to alter the gut microbiota is fecal microbiota transplantation (FMT). In a study that evaluates the efficacy and safety of FMT treatment for SLE patients, the researchers conducted a 12-week clinical trial offering 20 SLE patients with oral encapsulated fecal microbiome from healthy donors. The capsulized FMT treatment was given to the patients once a week at week 0, 1 and 2. Their blood and stool sampling was collected at week 0, 1, 2 4, 8 and 12 for analysis. The researchers found a significant reduce of the SLEDAI-2K scores for the patients. Also, they found that FMT induced a partial shift of the patients gut microbiota profile towards the microbiota profile of healthy donors, with a gradually increase of Firmicutes to Bacteroidota ratio. In addition, FMT increased the amount of short-chain fatty acids (SCFAs) in SLE patients. From the perspective of immunological effects of FMT, the researchers found an improvement in systemic immune-inflammation profiles of SLE patients after the FMT treatment. The result supported FMT as a practical, safe, and effective therapy for SLE patients [8]. Thus, alteration of the dysregulated microbiome can be crucial to SLE treatment.

3. Dermatomyositis (DM)

Dermatomyositis (DM) is a chronic autoimmune disorder that affects not only the skin but also other organ systems like muscles, joints and the respiratory system. The disease can affect both adults and children, and the estimated incidence of the disease is 9.63 cases per million. The most susceptible age is beyond 40 for adults and around 5-12 for children. Risk factors for DM includes exposure to UV light, virus infection, use of drug and unhealthy lifestyles related to smoking and consuming alcohol [9].

According to a study comparing the 16S ribosomal RNA of fecal samples from 36 DM patients and 26 health controls, the DM patients had an increase in Bacteroidetes to Firmicutes ratio like that of the patients of SLE. They also had an increase in Proteobacteria and a decrease in Actinobacteria. Beyond the phylum level, they were also more abundant in Streptococcus, Lachnoclostridium, and Tyzzerella 3 and 4 while less abundant in Bifidobacterium, Christensenellaceae R-7 group and Anaerostipes compared to the health controls. However, the researcher indicated that these differences were not significantly associated with the DM diseases [10]. Overall, the difference observed between DM patients and health control microbiota at the phylum level does indicate some

correlation of microbiota dysbiosis and the develop of DM, although the result does not provide a strong support for the difference at the genus level.

As a type of idiopathic inflammatory myopathy (IIM), DM can be treated with low dose of IL-2 to regulate the dysbiosis of intestinal microbiota. In a study evaluating the effects of IL-2 on gut microbiota, the researchers injected 1×106 IU of IL-2 to 13 IIM patients and 52 healthy controls once every other day for 12 weeks. Three months after the treatment, they found 12 of the 13 patients had responses and showed improvements in many characteristics such as muscle enzymes, and extra muscular activity. Regarding the effect on the microbiota, no significant change in alpha and beta diversity are found in the bacteria after treatment, but the comparative analysis indicated a significant increase in Lachnospiraceae_UCH-004 and Pseudobutyrivibrio genus for the IIMs patients after treatment. The study supported that low-dose of IL-2 can induce beneficial taxa with the potential to maintain the gut environment in a stable state [11]. As a result, low-dose of IL-2 may be a powerful tool targeting the microbiota for DM therapies.

4. Rheumatoid Arthritis (RA)

Rheumatoid Arthritis (RA) is a chronic inflammatory and autoimmune disease with a prevalence rate of 0.5-1.1% in North America. The disease has a negative effect on the synovium, and can lead to symptoms like joint damage, bone destruction and severe disability. Although the specific cause of RA is not known, many risk factors are predicted to trigger the disease, such as genetic factors, smoking, infectious agents, hormonal factors, and dietary factors [12].

According to a study comparing the circulating microbiome signatures of RA patients to that of the healthy controls by 16sRNA amplification of bacteria in the blood sample, the two groups do not show difference at the phylum level. For both the patients and health controls, the bacterial DNA is dominated by proteobacteria, followed by Firmicutes, Bacteroidetes and Actinobacteria. However, significant differences are shown at the genus level. The microbiome of healthy blood samples has Corynebacterium 1, Serratia, Streptococcus, Pseudomonas, Anaerococcus, Staphylococcus, and Achromobacter in the order of decreasing relative abundance. In contrast, the microbiome of blood samples from RA patients is dominated by Halomonas, followed by Anaerococcus, Pseudomonas, Corynebacterium 1, Shewanella, and Lachnospiraceae NK4A136 group [13]. The data indicates that the RA patients share similar bacterial genus with the healthy controls in their blood sample but the relative abundance for each of them is quite different. Thus, such a dysbiosis of microbiome community may have harmful effects and remodulate them back to a healthy level of abundance may be a potential treatment for the disease.

Probiotic supplementation may be a potential therapy modulating the microbiome dysbiosis for the RA patients. In a clinical trial treated RA with probiotic supplements, 60 RA patients are assigned into two group. Patients in experiment group were given probiotic supplement, and patients in control group were given placebo containing only starch but no bacteria. After 8 weeks of treatment, the researchers recorded the number of tender and swollen joints of the patients based on 28-joint count, VAS for pain and DAS-28 for assessment. Blood samples of the patients are also collected at week 0 and week 8 for analysis. The results indicated that the probiotic group showed improved DAS-28, decreased levels of serum insulin, HOMA-B as well as hs-CRP levels compared with the placebo group [14]. Since high HOMA-B and hs-CRP level can be markers of RA diseases, a decrease in these indexes supported the beneficial effects of probiotic supplements. Consequently, probiotic regulation may be potential target for further research of RA therapy in the future. However, since the study find no influence of the probiotic supplements on some other assessments such as glucose homeostasis parameters and oxidative stress [14], a combination therapy of probiotic with other complementary treatments that help regulate the glucose homeostasis and oxidative stress may have better therapeutic effects.

5. Type I Diabetes (T1D)

Type I diabetes is caused by an over activation of T cell which cause the production of antibodies targeting autoantigen such as beta cell which express receptor for insulin. As beta cell are destructed by the immune system, the insulin in the blood cannot be bring into the cell and thus lead to diabetes. Also, among the CD4+ T cells, the Th17 subset of cells produce IL-17 proinflammatory cytokines and help to activates other immune cells, while the Treg subset functions to regulate and suppress the immune responses. An imbalance between these two opposing subsets of T cells can also trigger autoimmune diabetes. Both the genetic and environment factors may play a role triggering T1D, and prevalence of T1D have a 7.4% annal increase, which leads to more concern of the public health [15].

Regarding the change in gut microbiome, children with positive islet‐autoantibodies shows a higher ratio of Bacteroidetes to Firmicutes ratio and a lower Shannon diversity. In addition, TD1 patients have less SCFAs-producing bacteria and lactate-producing bacteria. The abundance of Lactobacillus and Bifidobacterium also decreases for them. In contrast, the samples from healthy controls show more Prevotell [16]. Since SCFAs and lactates are very important for anti-inflammation and maintaining the homeostasis, lacking bacteria fermenting these components can may easily lead to dysbiosis and further trigger autoimmune diseases like T1D.

Just like for RA, probiotic intervention may also have the potential to alter the dysbiosis of microbiome and treat T1D. In a clinical study conducted in 2–12 years-year old children with new onset T1D, 90 children were allocated to either the probiotic group or placebo group randomly. The probiotic group was treated with multiple-strain probiotic supplements and the placebo group was treated with microcrystalline cellulose capsule. For assessment, the researchers recorded HbA1c, fasting C-peptide, blood sugar record, and insulin dose of the participants before and after three months of intervention. They found out that the reduction in HbA1c levels as well as total and bolus insulin dose are greater for the probiotic group than the placebo group. However, they did not find significant difference in the C-peptide levels or basal insulin requirement between the two groups. As a result, further clinical trials can be conducted to investigate the therapeutic effect of probiotic supplement on T1D [17].

6. Systemic Scleroderma (SSc)

Systemic sclerosis (SSc) is a multisystem connective tissue disease with two subtypes classified by the affecting body parts. Systemic sclerosis (lcSSc) affects only the face, neck and the area distal to elbows and knees, while diffuse cutaneous systemic sclerosis (dcSSc) also affects upper arms and thighs. The prevalence of SSc varies among different geographic region with an increase incidence over the last several decades. Both generic and environmental factors are responsible for the occurrence of SSc, and female has a much higher risk of developing SSc compared to male with a ratio of 7:1 [18].

When comparing the gastrointestinal microbiota with the health control, patients with SSc have a significant decrease in Bacteroidetes, which involves the commensal genera Bacteroides that is supposed to protect the host against pathogens and mucosal inflammation. More specifically, patients with SSc are depleted in Faecalibacterium, Clostridium, and Bacteroides, but are enriched in Fusobacterium, Ruminococcus, uncommon γ-Proteobacteria, and Erwinia in compare to the health controls. In addition, the microbiota profile also varied among SSc patients. Patients with mild GIT symptom have more Clostridium, while patients with moderate-to-severe GIT symptom have more Prevotella. Also, patients with milder constipation symptom have more Lactobacillus than those with severe constipation symptoms [19].

Just like for SLE, FMT can also improve dysbiosis of microbiota and treat SSc. In a study that try to determine the effects of FMT in SSc, the researchers randomly assigned 10 patients into either the FTM group or the placebo group and conduct a double-blind clinical trial for 16 weeks. After intervention, three of the five patients in the FMT group had an improvement in both upper and lower GI symptoms with a reduction in the total UCLA GIT score, and the condition continued up to week

16. Besides GI symptoms, the researchers also found more patients in the FMT groups reporting improvements in bloating, diarrhea and fecal incontinence in compare to those in the control group. In addition, in contrast to the control group, patients in FMT group had an increase in the Firmicutes phylum as well as alternation in the relative abundancies of IgA and IgM coated bacteria [20]. Although the sample size in this study is too small to draw strong conclusion, FMT may still be a potential therapy given the improvements of SSc-related symptoms in the patients.

7. Vitiligo

Vitiligo is a common depigmenting skin disorder that affects 0.5–2% of the population worldwide. The disorder is caused by the selective loss of functional melanocytes that results in pigment dilution in the affected skin region. Possible mechanisms behind the disease may related to autoimmune responses, oxidative stress, increase inflammatory mediators and loss of melanocyte, which involves both arms of the immune system [21].

In the comparison of gut microbiome from vitiligo patients and the heathy control, the researchers found a lower gut microbial alpha-diversity for patients with vitiligo, as well as an increase in Firmicutes-to-Bacteroidetes ratio in the stool sample. The two groups show no difference in bata-diversity of gut microbiome. When it comes to the comparison of skin microbiome, swab sample of both the non-lesion (NL) and lesion (L) vitiligo skin show greater alpha-diversity than the swab sample of healthy control skin. At the phylum level, the surface of NL vitiligo skin shared similar microbiota composition with healthy control skin. However, the swab sample of L vitiligo skin shows a decrease in Firmicutes compare to the NL skin due to a reduce in Staphylococcus and Cutibacterium, which may activate the innate immune system. Also, the L site of vitiligo skin shows an increase in Proteobacteria phylum compare to that in the NL sites and the healthy skin, which is associated with inflammation [22].

Although there are not sufficient data from clinical trials evaluating the therapeutic potential of probiotic and FMT on vitiligo, the use of probiotic to induce regulatory T cells can be a possible therapy for vitiligo. The regulatory T cell is a subset of helper T cell that suppress immune responses. Given autoimmune diseases happen when the immune system fails to build up tolerance and attack autoantigen, suppression of the overactivated immune system by Treg can help alleviate autoimmune diseases. Study supports that probiotics like B. infantis can stimulate human dendritic cells that selectively enhance the expression of FoxP3 in naïve lymphocytes, which is a marker for the Treg cells. Since regulatory dendritic cells that express high levels of IL-10 and TGF-β can directly covert the conventional T cells into FoxP3+ Tregs, B. infantis should be effective for Treg induction. Furthermore, B. infantis turns out to be effective in treating a series of experimental autoimmune diseases like inflammatory bowel disease, thus it is reasonable to expect the application of B. infantis to vitiligo therapy in the future [23].

8. Conclusions

Autoimmune disease is caused by the immune system attacking the host self-antigen, and it may be closely corelated with the host microbiota given dysregulation of microbiota is found in patients of many autoimmune diseases. At the phylum level, SLE, DM and T1D shows an increase in Bacteroidetes to Firmicutes ratio, while SSc and vitiligo shows an opposite trend of decreasing in Firmicutes relative to Bacteroidetes. Bacteroidetes and Firmicutes are very diverse phylum containing a wide range of bacteria with different functions and properties, so both phyla must contain bacteria that promote immune responses like inflammation as well as those that suppress these immune responses. As a result, the relative abundance and patterns of these two phyla shown in different types of autoimmune diseases can be quite different and no strong conclusion can be drawn regarding specific characteristics of Bacteroidetes to Firmicutes ratio for autoimmune diseases discussed in this paper. However, given five of the six autoimmune diseases listed above shown alternation in the

Bacteroidetes and Firmicutes ratio, it is very likely that an imbalance between Bacteroidetes to Firmicutes is closely related to autoimmune diseases. Also, all six diseases shown alternation in relative abundance of microbiota at the genus level, which further suggest a crucial relationship between microbiota and autoimmune diseases.

Table 1. Alternation of microbiota profile at genus level in six autoimmune diseases

Autoimmune Diseases	Increase	Decrease
Systemic Lupus Erythematosus	Rhodococcus, Eggerthella, Klebsiella, Prevotella, Eubacterium, Flavonifractor	Dialister, Pseudobutyrivibrio
Dermatomyositis	Streptococcus, Lachnoclostridium, Tyzzerella 3 and 4	Bifidobacterium, Christensenellaceae R-7 group and Anaerostipes
Rheumatoid Arthritis	Profile show Halomonas, Anaerococcus, Pseudomonas, Corynebacterium 1, Shewanella, and Lachnospiraceae NK4A136 group in the order of decreasing relative abundance	
Type 1 diabetes	Bacteroidetes	Firmicutes, SCFAs-producing bacteria, lactate-producing bacteria, Lactobacillus, Bifidobacterium
Systemic Scleroderma	Fusobacterium, Ruminococcus, uncommon γ-Proteobacteria, Erwinia	Faecalibacterium, Clostridium, Bacteroides
Vitiligo (L vs.NL skin)	Proteobacteria	Staphylococcus and Cutibacterium

Fecal microbiota transplantation and probiotic supplement are the most used treatment to remodulate the microbiota for patients with autoimmune diseases, such as FMT for SLE and SSc, and probiotic supplements for RA and T1D. Although the probiotic treatments may not be powerful enough to bring improvements in all of the symptoms assess in the clinical trial, the results do supports that these treatments have a therapeutic effect relieving some symptoms of the studied autoimmune diseases. Also, probiotics like B. infantis are predicted to be able to induce regulatory T cells for the host to suppress the immune responses. It turns out to be effective in a series of autoimmune diseases like inflammatory bowel disease, with the potential to be applied to more disease like vitiligo. Beyond FMT and probiotic supplement, studies also shows that low dose of IL-2 can regulate the intestinal microbiota for DM patients.

To further understand the role of microbiota in autoimmune diseases, future study may focus on the functions and effects of more specific types of bacteria in autoimmune diseases and try to predict possible causal relationship beyond the correlation. This may be helpful for the detection of more accurate target for microbiota treatment of autoimmune diseases and thus improve the efficacy of the treatment. In addition, a combination of probiotic therapy with the proper use of immunotherapy drug may be a target for future investigation to complementarily improve the therapy efficacy while alleviating the side effects of conventional therapy to normal immune functions.

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