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Gut microbiota in systemic lupus erythematosus pathogenesis: an in-depth view of mechanisms inside

Qifan Chen

College of Chemistry and Chemical Engineering, Xiamen University, Xiamen, Fujian, 361000, China

kexincao@mails.ccnu.edu.cn

Abstract. Systemic lupus erythematosus (SLE), an autoimmune disease that is known to be prototypic, brings systemic influence via abnormal production of autoantibodies targeting nuclear acid, possesses highly sophisticated pathogenesis related to genetic and environmental factors. In current studies, gut microbiota draws increasing attention from researchers as it is considered to trigger local and systemic immune responses. Researchers have detected a wide range of alterations happen in SLE cases and revealed a series of potential mechanisms of how microbiome and metabolites are involved in the development and progression of SLE: translocation of pathobionts out of their normal niches; molecular mimicry inducing cross-activity to initiate autoimmune response; and epitope spreading to widen the target of autoantibodies. Based on the understanding of the microenvironment, treatments aiming at adjusting gut microbiota are proposed, including but not limited to the usage of probiotics or prebiotics, narrow-spectrum antibiotics or phages, dietary management and faecal microbiota transplantation. In this article, research progress showing the connection of gut microbiome with SLE and potential mechanisms as well as suggesting more efficient therapeutic strategies for SLE are reviewed. Although more detailed pathogenesis mechanisms and theories of treatments remain unclear while integration of courses along with advanced techniques are required to reveal the complicated connection shown in clinical trials, research in this territory still shows a promising prospect.

Keywords: Gut Microbiota, Systemic Lupus Erythematosus, Dysbiosis, Immune Response.

1. Introduction

Systemic lupus erythematosus (SLE) is a typical autoimmune disease featuring abnormal production of various autoantibodies targeting components of cell nuclei in the patient's own body. The autoimmune responses lead to multisystemic chronic inflammation, vasculitis, deposition of immune complex, and vasculopathy. SLE often affects a variety of organs, including but not limited to skin, joints, kidneys, lungs, hearts, gastrointestinal tract, and nervous system, while the patients often experience periods of remission and exacerbation. SLE frequently appears among the first-degree relatives of patients, showing notably familial aggregation. Other organ-specific autoimmune diseases, including haemolytic anaemia, thyroiditis, and immune thrombocytopenic purpura, may also coexist with SLE in extended families, and concordance of this disease in identical twins is reported to be around 25–50% while dizygotic twins showed only approximately 5%, showing the important role of genetic factors in the

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predisposition of SLE [1]. However, the pathology of SLE is far more complicated, and the cases often show sporadic features. Demonstrable genetic predisposing factors cannot be found in most cases of the disease, indicating the effect of environmental and other unknown factors.

Various of researches have shown that infection of microbiota can act as a trigger of autoimmune response and subsequently cause several inflammatory diseases. For example, though the Th17 cells are essential for immune responses against extracellular bacteria and fungi, it was reported to show universal immunoreactivity towards fungi when induced by cross-reactivity to mucocutaneous pathobiont Candida albicans. Research on this atypical response indicated the direct connection between the protective role and pathogenic role of Th17 cells originating from T cell cross-reactivity, confirming that these features contribute to the manifestation and/or exacerbation of pulmonary inflammatory diseases [2]. Moreover, studies on SLE cases have reported notable association of infectious processes with onset of this disease, particularly infection caused by several types of human endogenous retrovirus and bacterial components that can probably trigger the activation of the immune system [3].

The results of this research inspired the researchers to take a gain of the microbial community carried inside by humans. Gut microbiota, located on barrier surface of mucosa, comprise an extraordinarily complicated community of microorganisms along with their countless metabolites. Gut microbiota catabolizes indigestible dietary fibre, synthesizes essential vitamins, and also affects the host immune system with the constantly produced exogenous antigens, which act as signalling molecules, thus performing sustained interaction [4]. Gut microbiota is proposed to be a newly discovered factor in autoimmune diseases, since studies on faecal metagenomes revealed significant alteration in microenvironment between healthy controls and SLE patients, including untreated patients and post-treated ones. Certain species of microbes were reported to enrich in patient's intestine and show a declination after treatment, which has partially demonstrated the relevance between SLE and change of density and variety of gut microbiota, suggesting intestinal dysbiosis as an auto-immunogenic and proinflammatory trigger in lupus [5].

In this review, the evidence revealing the role played by the microenvironment in the onset and exacerbation of SLE and the potential mechanisms involved in the processes of this disease are summarized based on advances in this territory. Additionally, the perspective of therapeutic strategies in the future and the existing treatments towards SLE referring to the theory of gut microbiota will be presented, together with newly reported clinical trials.

2. Role of gut microbiota in SLE

2.1. Alteration of gut microbiota in SLE cases

The link between characteristics of intestinal dysbiosis and SLE has been studied for years, mostly based on observational case-control reports. Additionally, longitudinal studies involving both human and murine models are carried out.

The composition of the microbiome in the intestinal environment of SLE patients has been reported to be different from healthy controls (HCs), with the alpha-diversity drastically decreased regarding all metrics, including quality, quantity, and phylogenetic awareness, with decreased Firmicutes/Bacteroidetes (F/B) ratio in comparison. Studies on differentially abundant taxa indicated a significant decline in Tenericutes in gut microbiota in SLE patients, while the Tannerellaceae family, Alistipes genus (mostly A. onderdonkii), Flintibacter, and Parabacteroides genus were abundant comparatively. Moreover, distinct features can be observed between inactive SLE patients and active ones. In addition to significant differences in beta-diversity, SLE patients with high activity of disease exhibit a lower F/B ratio, and six taxa showing differential abundance compared to the inactive group, including decreased Bacilli class, Lactobacillaceae families and Ruminococcaceae, together with increased Desulfovibrio piger, Bacteroides thetaiotaomicron, and Ruminococcus gnavus species. These signatures of dysbiosis have subsequently been proven to be stable over time.

As for the murine studies on gut microbiota during the progression of lupus, while significant difference in F/B ratio has not been found in both control (CO) and pristane-induced-lupus (PIL) mice,

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some of the bacterial population in PIL mice are revealed to have altered in the endpoint of the disease. When analysing results collected from comparisons between SLE patients and HCs to murine data, five differently abundant biomarkers are revealed, specifically increased Alistipes genera, Tannerellacea family, Parabacteroides and Bacteroides, decreased Tenericutes in both SLE patients and PIL mice when compared to HCs and COs, suggesting the common features of the linkage between SLE and disrupted gut microbiota across species [6].

2.2. Regulating mechanism of gut microbiota in SLE

Universally declined diversities detected in SLE cases suggest the potential mechanism of how gut microbiota complexity regulates normal eubiosis. Mutual complementation supply and containment play crucial roles in normal eubiosis. Increasing evidence also supports the assumption that gut microbiota with reduced diversity caused by overuse of antibiotics, inappropriate diet, or environment as well as individual sanitation contributes to immunopathogenesis in cases [7]. Several widely-accepted mechanisms involved in this process are reviewed here.

2.2.1. Pathobiont translocation. The gut barrier plays an essential role in preventing the invasion of antigens originating from microbes normally located in the intestine. Therefore, studies have been put forward to reveal the potential correlation between translocation of gut commensals and systemic autoimmune activities in SLE. Research on mice with genetic background predisposing to autoimmunity suggested that the presence of Enterococcus gallinarum can negatively affect functions of the barrier by down-regulating correlating ileal molecules, mucus layer, and the antimicrobial defence while up-regulating molecules related to inflammation, which is closely connected with immune response in SLE. During this process, bacterial proliferation in mesenteric lymph nodes (MLNs), mesenteric veins, liver and even spleen can be observed in model mice. These translocations reduce when antibiotics, namely vancomycin or ampicillin is applied to the cases, which prevents mortality while also eliminating pathogenic autoantibodies and T cells. Similarly, when pathobiont translocation happens in autoimmune-prone mice, autoantibodies can be induced and cause death, while this can be prevented by the intramuscular vaccine. In longitudinal studies, faecal albumin and calprotectin are reported to increase in stool analyses from SLE patients, indicating impaired gut barriers, and the majority of liver biopsies from patients with serologic features of lupus, specifically with SLE and autoimmune hepatitis (AIH), are identified positive for E. gallinarum, which indicates the same process of bacterial translocation happening in susceptible humans and thus driving autoimmune pathogenesis [8]. Although whether 'gut leakage' is an initiating factor in SLE cases remains unknown, dysbiosis can certainly cause an impaired gut barrier, which conversely facilitates the translocation of gut commensals [9].

2.2.2. Molecular mimicry. In genetically susceptible individuals, gut commensals are believed to initiate and propagate autoimmune activity via molecular mimicry. This mechanism enables them to agitate autoreactive T/B cells with orthologs or sometimes mimotopes of autoantigens. During the process of the immune response, presentation process as well as recognition of antigens comprised of microbial peptides can be influenced by genetic factors (namely alleles HLA-DRB1 shared epitopes). Therefore, auto-immunogenicity aiming at the bacterial component can contribute to autoimmune diseases by being translated into relational pathogenesis. Roseburia intestinalis, a gut commensal commonly found in human gut, is reported to express non-orthologous mimotopes of antiphospholipid syndrome (APS) autoantigen β2-glycoprotein I (β2GPI), which performs cross-reactivity with T and B cell autoepitopes in β2GPI, inducing anti-β2GPI antibody response, during which the corresponded pathogenic monoclonal antibodies perform cross-reaction with the bacterial mimotopes produced by R.int. This mechanism contributes to β2GPI-specific lymphocytes and autoantibodies induced by immunization [10]. Additionally, infection caused by E. gallinarum carrying orthologue of β2GP1 also triggers the corresponding antibody response [8]. Similarly, cross-reactivity happens also in between Ro60-containing bacteria strains on skin and mucosal and correspondingly specific CD4 memory T cell clones, as commensal Ro60 ribonucleoproteins can be immunoprecipitated from sera originating from

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lupus patients identified as anti-Ro60–positive. Studies on model mice mono colonized with gut commensals carrying Ro60 ortholog showed spontaneous initiation of anti-human Ro60 T and B cell responses and deposits of glomerular immune complex, supporting the assumption that bacterial peptides mimicking specific human epitope can lead to abnormal production of corresponding antibodies in genetically predisposed individuals, together with initiation of chronic autoimmunity [11].

2.2.3. Epitope spreading. In addition to cross-reactivity induced via molecular mimicry mechanism, extended immune reactions also act as a typical phenomenon presenting the 'misleading effect' of bacterial molecules on the immune system during a series of autoimmune responses. Epitope spreading of anti–citrullinated protein antibodies (ACPAs) in serum is considered to be a crucial molecule in the pathogenesis of rheumatoid arthritis (RA). Studies have shown that during the maturation of affinity, clonally related B cells are detected to accumulate different somatic hypermutations, which alters the antibody paratope, and hence initiates the epitope spreading together with polyreactivity of ACPA response in RA cases [12]. This suggests the link between microbes and epitope spreading-related pathogenesis: in the process of inflammation, endogenous epitopes are released by dead cells of invading microbes, which plays similar role with orthologue/mimotope carrying microorganisms in triggering autoimmune response and subsequently production of autoantibodies. The capability of binding with wider range of epitopes is developed via epitope spreading, initiating broader self-responses. According to a study on non–SLE-prone mice, the immune response against human Ro60 protein not only results in the production of anti-La and anti-Ro52, and also a wide range of antibodies including anti-SmA, anti-SmB, and anti-SmD, which suggest epitope spreading as an essential mechanism in producing autoantibodies [13]. Collectively, the hypothesis is supported by increasing studies that molecule mimicry together with epitope spreading are most likely to play crucial roles in pathogenesis of SLE, and might be the key to revealing further and more detailed mechanisms linking gut microbiota with autoimmunity.

3. SLE treatment targeting gut microbiota

3.1. Probiotics/prebiotics

Live microorganisms that are reported to be beneficial to the host's health in inappropriate management, namely probiotics, can be given in adequate quantity and help to improve the intestinal environment when staying in specific niches. Research shows that when a combination of 5 Lactobacillus strains (L. oris, L. reuteri, L. johnsonii, L. rhamnosus, and L. gasseri) is used to compensate for the depletion of Lactobacillus spp. among gut microbiome, improvement on renal function and prolonged lifespan can be observed in lupus nephritis model mice. Studies also revealed that increasing Lactobacillus colonization can reverse 'gut leakage' in cases, and also cultivate an anti-inflammatory gut environment since it regulates the production of several interleukin [14]. Additionally, prebiotics, which represent a variety of nutrients (e.g. oligosaccharides) available for microbes, can be added to gut environment to nourish the beneficial bacteria and help to reconstruct a balanced community.

The advantages of using rather a simple composition of probiotics as a treatment include controllability and lower difficulty in recovering when the trial is proven to be inappropriate since corresponding antibiotics can be introduced and adjust the microbes precisely. However, it is impossible for a method involving simplified probiotics to be universally effective for all cases of a specific autoimmune disease due to the complexity of the microenvironment and various interaction mechanisms that still remain unclear, which is proved by a large number of clinical studies presenting inconsistent and even contradictory results.

3.2. Antibiotics/phages

According to the accumulating evidence, invasion or excessive multiplication of specific strains of bacteria might play a crucial role in arousing autoimmunity [7,10,12]. Therefore, with the ability to suppress particular commensals and pathobionts, antibiotics and bacteriophages are considered to be

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potentially efficient methods in treating intestinal dysbiosis. Studies have shown that oral intake of mixed antibiotics or single antibiotic vancomycin given to lupus-prone mice can reduce harmful strains from gut microbiota and attenuate SLE-like disease, ameliorate systemic autoimmunity as well as kidney histopathology, remove Lachnospiraceae and increase relative abundance of Lactobacillales. In this process, vancomycin increases the functions of the intestinal epithelium barrier, hence preventing lipopolysaccharide from entering the circulation [15].

Although antibiotics can provide beneficial effects on gut microbiota when used appropriately, they might also disturb the fragile microenvironment in patients' intestines, aggravate gut dysbiosis, and sometimes lead to the development of drug-resistant microbes. Therefore, narrow-spectrum antibiotics are in urgent need to perform target-specific adjustments on harmful strains in gut microbiota and avoid causing disorder

3.3. Dietary management

The idea of manipulating intestinal microenvironment, microbial metabolism and autoimmune response via diet introversion, specifically an anti-inflammatory diet, is considered to be a soft approach compared to direct suppression, elimination, or transplantation aiming at precise commensals. The potential of dietary management has already been primarily proved. For example, retinoic acid as a dietary supplement is reported to reverse the alterations which is related to lupus in functions of the microenvironment in lupus-prone mice that deviated from the control, thus improving lupus symptoms [16]. Moreover, the Mediterranean diet, which features abundant fibre with unsaturated fatty acid, has been proven to have a significant relation with several intestinal microbes. Faecal analysis suggests that a higher Mediterranean diet score (MDS) often results in a lower concentration of Firmicutes and Lachnospiraceae, together with a higher level of several strains, specifically Bacteroidetes, Prevotellacea, along with Prevotella. This may be accompanied by the result of faecal analysis showing higher levels of propionate and butyrate when MDS is especially high (MDS ≥ 4). Considered a beneficial phenotype for anti-inflammatory, it provides a potential methodology for treatments aiming at RA and SLE [17].

3.4. Faecal microbiota transplantation (FMT)

Being able to contribute to the abundance along with a diversity of gut microbiota, reconstruct balanced states of intestinal micro ecosystem via transplanting a complete set of commensals collected from strictly selected healthy donors to the recipients suffering from intestinal dysbiosis, FMT has already been involved in the treating methods of many intestinal diseases related to dysbiosis in the gut environment. The idea of applying FMT as a therapeutic method to SLE cases has been put forward for years and is now supported by the first clinical trial. Studies during which oral encapsulated faecal microbiome is given to SLE patients with estimated high levels of SLE activity in three weeks presented firstly no serious adverse events, suggesting the safety of this method. Subsequently, significant enrichment of bacteria strains producing short-chain fatty acids (SCFAs), reduction of bacterial taxa related to inflammatory reaction, raised content of SCFAs in the intestine and declined levels of the inflammation-related index in peripheral blood are observed at the 12th week compared to baseline. The patients' microbiota presents specific signatures both before and after treatment, indicating that by regulating gut microbiota. FMT is primarily considered to be a safe, practicable, and promising therapeutic strategy in SLE cases [18]. Nevertheless, the more detailed mechanism of how FMT transfers the gut microenvironment remains unknown, and further research along with clinical trials is also required to inspect the feasibility of FMT application. Still, this approach sheds light on the future of new treatment methods.

4. Conclusion

Studies on gut microbiota have partially revealed the potential mechanisms of how the disturbed inner community of microbes negatively affects the host by setting off autoimmunity, thus providing not only a better understanding of the gut microenvironment but also more detailed features of the operation of the immune system. However, many questions are left to be answered. For example, the exact range of

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bacteria strains that affect autoimmune response precisely when multiply excessively remains unknown, and the specific corresponding connections between bacterial molecules and the production of antibodies require more animal research along with clinical trials to unveil. Notably, research on role plays by gut microbiota in SLE should never be considered as an isolated approach, since sophisticated interactions happen constantly between host and microenvironment. The former element can be influenced by genetic factors, diet preference in the long term, the present state of the immune system and sometimes other chronic diseases, while the latter stands for communities that comprise mycobiome, virome, and even parasites with tremendous complexity, together with interaction among different strains, effect on intestinal barrier related to the translocation process, and stimulation to the host immune system caused by various of metabolite, represented by epitope spreading. Moreover, external factors, specifically drugs, prebiotics and antibiotics, can also add to this complicated system. Therefore, to promote further research in this territory, an approach should be made to integrate different courses, including but not limited to the host genome, immunology, microbiology, clinical medicine and metabonomic study. This will largely rely on the innovation of techniques and improvement of bioinformatic algorithms, which will enable wider application of studies involving multiple models and more sophisticated analysis of cautiously collected data in the future.

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