New Pathophysiology Insight of Gut Microbiota's Influence on Systemic Lupus Erythematosus: A Brief Review

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ABSTRACT

Systemic lupus erythematosus (SLE) is a commonly found chronic autoimmune disease that affects multiple organs and systems. According to a new study, commensal gut microbiota promotes chronic autoimmunity in SLE patients with a lower Firmicutes/Bacteroidetes ratio. It has to do with the activation of inflammatory mediators such as toll-like receptors (TLRs), NOD-like receptors, adaptive immune response, and antimicrobial peptides mucins, defensins, and immunoglobulin A production. Aside from that, a decreased Firmicutes/Bacteroidetes ratio may cause T helper cells and regulatory T cells to become activated, both of which are linked to autoimmune activation in SLE. Theoretically, the immunomodulatory influence of food components in immune system activation has been the focus of nutrition for SLE patients, but probiotics and prebiotics have also been shown to dramatically enhance gut microbiota associated to SLE.

Keywords: Autoimmune, chronic disease, gut microbiota, systemic lupus erythematosus.

Published Online: January 24, 2022

ISSN: 2684-5199

DOI : 10.24018/ejbio.2022.3.1.321

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I. INTRODUCTION

Systemic lupus erythematosus (SLE) is a commonly found chronic autoimmune disease characterized by diffuse connective tissue disorder that affects multiple organs and systems (Schulz & Derk, 2009). SLE has a wide range of incidences across countries, with the global incidence in 2017 ranging above 50 to 241 per 100,000 adults (Rees *et al.*, 2017). Aside from that, (Mu *et al.*, 2017) reported that there were 20 to 200 cases per 100,000 patients among Asians, which affecting primarily women (but also quite common in males, children, and those over 50 years old), and targeting a variety of organs including the heart, kidney, skin, lung, and gastrointestinal tract (Mu *et al.*, 2017; Han *et al.*, 2015). This form of autoimmune disorder may recur and go into remission again, and typically holds of huge number of autoantibodies in the body. Apparently, the etiology of SLE is still unknown, but it has been linked to a variety of environmental (e.g., drug exposure and UV radiation), hormonal, and genetic variables.

Nonetheless, the present understanding of the relationship between gut microbiota and SLE has been demonstrated in a lupus-prone mouse model (Bandre *et al.*, 2021). The gut microbiome has been recommended as another crucial component. However, an insufficiency of knowledge continues to cast doubt on proofing the impact of gut microbiota on SLE (Mahajan *et al.*, 2021). There are various possibilities on how the gut microbiota interacts with the host and how is it related with SLE, but still no definitive theories have been found. Thus, the purpose of this review is to present the current ideas and thoughts of gut microbiota's role on SLE.

II. GUT MICROBIOTA AND AUTOIMMUNE

In theory, the human gastrointestinal system comprises of more than 100 trillion microorganisms, the most of which are found in the colon. Dysbiosis (changes in gut microbial population) has been linked to several autoimmune and chronic inflammatory disorders, including rheumatoid arthritis, type 1 diabetes, inflammatory bowel disease, and, most recently, SLE (Hevia *et al.*, 2014). Changes in the microbiota are influenced by a variety of factors, including gender, age, nutrition, race, stress, lifestyle (smoking habit, alcohol intake), medicine (antibiotics), and infections (Neuman & Koren, 2017). According to research by Perry *et al.*, a number of microbiota (such as *Clostridium clusters XIVa & IVa*, *Lactobacillus*, *Eubacterium*, *Bacteroidetes*, *Firmicutes*, and *Bifidobacterium*) are assumed to be connected to gastrointestinal physiology (Perry *et al.*, 2014). In the human body system, the gut microbiota plays a role in immune activation. When the gut microbiota is out of balance, it can stimulate innate immune responses including toll-like receptors (TLRs), NOD-like receptors, adaptive immunological responses, and the release of mucins, antimicrobial peptides, defensins, and immunoglobulin A (IgA), which can help the immune system mature (Hollister *et al.*, 2014). The gut microbiota also had a role in the regulation and development of Peyer patches, germinal centers, and mesenteric lymph nodes (MLN), according to a research by (Kamada *et al.*, 2014). Aside from that, the gut microbiota controls the growth of effector T cells and the production of cytokines that impact the T helper (Th17) cells and regulatory T (Treg) cells, all of which have a key role in autoimmune activation in SLE (Kamada *et al.*, 2014).

III. GUT MICROBIOTA IN SLE

Systemic lupus erythematosus has been known as a systemic autoimmune disease characterized by the development of hyperactive and aberrant autoantibodies against nuclear and cytoplasmic antigens, as well as the activation of auto reactive inflammatory T cells and atypical proinflammatory cytokine release (Mu *et al.*, 2015). Wei *et al.*, (2019) stated that, the gut microbiota may play a critical role in SLE patients which can be seen by a much-reduced *Firmicutes/Bacteroidetes* ratio (Wei *et al.*, 2019). Ma *et al.* also proposed that the commensal gut microbiota may be a trigger for chronic autoimmunity in SLE patients (Ma *et al.*, 2019). They also discovered that the feces of lupus mice can promote the development of anti-dsDNA antibodies and an inflammatory immunological response in recipient germ-free mice, which would upregulate the expression of SLE susceptibility genes (Ma *et al.*, 2019).

Additionally, the relative abundance of *Firmicutes* is lower (Fig. 1c) in SLE patients, while that of *Bacteroidetes* is higher, indicating a lower ratio of *Firmicutes* to *Bacteroidetes* than in healthy people (Hevia *et al.*, 2014). The overgrowth of *Ruminococcus gnavus* (RG) in the gut microbiota of a few female SLE patients differing in disease activity was initially described by Azzouz *et al.* RG expansions in the gut reflected the severity of disease activity and were common in SLE patients (Azzouz *et al.*, 2019).

According to (Mu *et al.*, 2015), increased gut permeability (leaky gut) and gut microbial product translocation have been shown to favor lupus formation and disease progression. Increased intestinal permeability and *L. reuteri* translocation into inner organs were found in TLR7-transgenic spontaneous lupus mice (Fig. 1a) (Zegarrra-Ruiz *et al.*, 2019). As a result, *Enterococcus gallinarum* has been found in the mesenteric vein, gut-draining lymph nodes, livers, and spleens (Fig. 1b) (Manfredo *et al.*, 2018). The ileal barrier was similarly compromised in *E. gallinarum* monocolonized mice, as demonstrated by downregulated mucus layer and antimicrobial defense markers (Manfredo *et al.*, 2018). Both species have the ability to activate pDCs and secrete interferon (IFN- α), which are major factors to SLE pathogenesis (Fig. 1a, d). Even if the SLE patient does not have any gastrointestinal symptoms, an impaired gut barrier is found in SLE patients (Thim-Uam *et al.*, 2020). The high quantity of serum lipopolysaccharide (LPS), a cell wall component of gram-negative bacteria, which may be eliminated by antibiotics (e.g. vancomycin) therapy, together with the relief of lupus-like manifestations in MRL/lpr mice, may imply enhanced gut permeability in SLE patients (Mu *et al.*, 2017).

Moreover, the plasma LPS level in SLE patients is strongly linked with anti-dsDNA antibody titers in the blood (Ogunrinde *et al.*, 2019). Other indicators linked with gut barrier insufficiency, such as fecal calprotectin levels, serum soluble CD14a, and serum 1-acid glycoprotein, have also been found to be elevated in SLE patients (Azzouz *et al.*, 2019). (Lopez *et al.*, 2016) discovered that SLE patients have decreased levels of the *Firmicutes* to *Bacteroidetes* ratio

(Synergistetes). Consequently, Synergistetes has the ability to lower blood levels of interleukin (IL-6) (a proinflammatory cytokine) and may induce B1 cells to generate natural protective IgM anti-phosphorylcholine under physiological settings. This can be accomplished in a number of ways [clearing of apoptotic cells and cellular debris, elimination of oxidized lipids, inhibition of mitogen-activated protein kinase (MAPK) activation, and other proinflammatory mediators] (Gronwall *et al.*, 2012). Aside from that, patients with SLE had a lower abundance of *Lactobacillaceae* and a higher richness of *Lachnospiraceae* (Mu *et al.*, 2015).

Lactobacillus spp. and *Lactobacillus reuteri* have recently been shown to improve kidney function in rats suffering from lupus nephritis. Treatment with *Lactobacillus* spp. repaired intestinal permeability (altered before the beginning of nephritis), lowered inflammatory cytokines (i.e. IL-6 and IL-18), and boosted anti-inflammatory cytokines (i.e. IL-10, Transforming growth factor (TGF- β)) and Tregs, according to the researchers. It also showed a reduction in IgG2a (one of the primary immunological deposits) and IFN- levels, indicating that renal impairment was improving. However, no such evidence was seen in male mice, indicating that the microbiome's effect is sexually linked and dependent, and implying a role for sex hormones in the gut microbiota's regulatory function on lupus (Mu *et al.*, 2017; Mu *et al.*, 2015).

IV. POTENTIAL TREATMENT FOR GUT MICROBIOTA IN SLE

A. Diet as Strategy on Gut Microbiota

The immunomodulatory influence of dietary components in immune system activation has been conceptually highlighted in the nutrition strategy for patients with SLE. Although little is known about the influence of diet on microbiota in SLE patients, there is some nutrition research that suggests that part of the dietary impact on SLE pathogenesis might be done by gut microbiota manipulation (Vieira *et al.*, 2014). Regrettably, there isn't enough evidence to say if a dietary intervention can help prevent SLE recurrences. A few studies from other diseases with dysbiosis have shown the function of many dietary components in balancing particular gut microbiota quantities, which might be applied to SLE.

Ley *et al.*, (2006) found a low-fat and low-carbohydrate diet can replace the gut microbiota balance by boosting the number of *Bacteroidetes* in SLE patients with high *Firmicutes/Bacteroidetes* ratios. Animal proteins and saturated fats in the diet have also been linked to a higher abundance of *Bacteroidetes*, according to (Yatsunenکو *et al.*, 2012). High consumption of whole grains, on the other hand, has been linked to a positive rise in *Firmicutes/Bacteroidetes* ratio in the gastrointestinal tract, and the administration of a low-fat/high-fiber diet has been linked to a positive increase in *Firmicutes* quantity (Martinez *et al.*, 2013; Wu *et al.*, 2011). De Filippo *et al.*, (2010) discovered that long-term intake of diets rich in whole grains, dietary fibers, and vegetables resulted in decreased levels of *Bacteroidetes* in African children, demonstrating the health advantages of whole grains through microbiota modification (De Filippo *et al.*, 2010).

Fig. 1. The pathogenesis of SLE from gut microbial. (a) & (c) SLE patients have a limited microbial diversity in their stomach, with the possibility of expanding their microbiome. (a) Microbiota can be translocated to MLNs and the liver when gut permeability is compromised. (b) *E. gallinarum* delivers ligands to the aryl hydrocarbon receptor (AhR), and (d) Proliferation of Th17 and Tfh cells is stimulated by activation of the AhR pathway, which leads to the generation of systemic autoantibodies. *E. gallinarum* causes plasmacytoid dendritic cells (pDCs) and hepatocytes to produce type I interferon (IFN). TLR7-dependent *L. reuteri* translocation increases the amount of pDCs and type I IFN expression, inducing SLE. Cross-reactive T and B cell responses are triggered by bacterial orthologs' molecular mimicry of human autoantigens, causing SLE.

Of fact, there is no other study in the literature that specifically evaluates the impact of the amount and type of lipids in the diet on the microbiota of people with SLE. Cuervo *et al* found no evidence of a link between lipids or saturate fatty acids in moderate levels in a well-balanced diet and fecal microbiota in an SLE cohort in a descriptive investigation (Cuervo *et al.*, 2015). In a previous study conducted recently, researchers found a link between fruit consumption, such as oranges and apples, and reductions in specified microbe populations in SLE patients (Cuervo *et al.*, 2015). It's crucial to remember that these fruits are natural sources of polyphenols and fibers with a significant potential for microbiota modulation. *Bifidobacteria* degrades particular phenolic chemicals, such as dihydrochalcones from apples, as well as dietary fiber, encouraging its proliferation. Given the immunomodulatory impact attributed to several strains of the genus *Bifidobacterium*, these types of alterations might be particularly interesting for SLE patients (Konieczna *et al.*, 2012). The *Bifidobacterium bifidum* LMG13195 strain, for example, increased the proliferation of Treg cells, a type of T-cell that promotes mucosal homeostasis (Lopez *et al.*, 2011). Another study discovered a correlation between dietary flavones and the levels of *Blautia* sp., a *Clostridium* cluster XIVa member. Because this microbiota is also involved in Treg cell development, boosting its growth through nutrition may be beneficial in restoring or maintaining immunological activation systems (Atarashi *et al.*, 2011).

Intriguingly, in animal models, a dietary therapy with vitamin A supplementation has demonstrated benefits in SLE pathogenesis, particularly in the decrease of both proteinuria and glomerulonephritis, and has been found to lessen symptoms generally (Hsieh & Lin, 2011). Another dietary intervention research found that retinoic acid (the active form of vitamin A - retinol) supplementation restored

decreased lactobacilli levels that had fallen during the development of SLE in an animal model (Cuervo *et al.*, 2015).

B. Probiotics or Prebiotics

Surprisingly, taking probiotics or prebiotics has been shown to increase gut microbial health in people with SLE. Another study found that long-term probiotic consumption may lower lupus severity by regulating inflammatory responses and reducing autoantibody synthesis (Esmacili *et al.*, 2017). When compared to microbiota isolated from healthy controls, microbiota isolated from SLE patient feces samples boosted lymphocyte activation and naïve CD4 + lymphocyte differentiation towards the Th17 subset (Lopez *et al.*, 2011), based on a study by López *et al.*, (2011). Furthermore, when the same proportions of *Bifidobacterium bifidum* LMG13195 (Bb) or a mix of two *Clostridia* strains (CI: *Ruminococcus obeum* DSM 25238 and *Blautia coccoides* DSM935) substituted 5, 10, or 30% of SLE gut microbiota, it was found that Bb and CI notably reduced CD4+lymphocyte over-activation and Th17/Th1 balance (Lopez *et al.*, 2011). Both BB and CI are well-known for their Treg inducing effects (Lopez *et al.*, 2011). Mike *et al.*, (1999) found that feeding mice a *Lactobacillus casei* (LC) diet from the time they were weaned might extend their lives and inhibit the growth of B220+ T lymphocytes in the spleen and mesenteric lymph nodes (Mike *et al.*, 1999). In addition, intraperitoneal injection of LC into mice dramatically reduced splenocyte proliferation and the B220+CD4-CD8-T cells accumulation, while boosting I-A-macrophages and macrophage colony-forming cells (M-CFCs) (Mike *et al.*, 1999).

Overall, while there is a paucity of data on SLE therapy based on gut microbiota strategy, the present evidence leads to a feasible SLE treatment method (Esmacili *et al.*, 2017).

However, the underlying processes causing the beneficial effects of a particular diet, prebiotics, or probiotics on SLE are yet unknown, and further comprehensive study is needed (Pigneur & Ruemmele, 2019).

V. CONCLUSION

According to this review, gut microbiota imbalance can cause gut barrier problems and microbial translocation, which leads to immune dysregulations such as IFN pathway overactivation and Th17/Treg imbalance. These conditions are linked to SLE pathophysiology by inducing self-tolerance breakdown and autoantibody production. Individualized gut microbiota management, such as dietary intervention and probiotic or prebiotic supplementation, might be a potential SLE therapeutic techniques in the future. However, more research is needed to assess the long-term benefit of the dietary strategy on SLE patients.

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