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Review Article

Systemic Lupus Erythematosus Managed by FMT

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Abstract:

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease. The manifestations of this disease are expressed as pathological disorders such as, lupus nephritis, seizures and memory problems etc. Etiology as well as promising modality for management of this disease is still ill defined. Recently focussed FMT therapeutic technique showed promise in controlling SLE and its variants in animal as well human models.

Keywords: autoimmune disease; sle types; mechanism; dysbiosis; management

Introduction

Systemic lupus erythematosus (SLE) is a chronic disease, a causal factor for developing inflammation in connective tissues throughout the body. In spite of technical advancement in medical diagnostics, the etiology of SLE is still found to be an enigma. This autoimmune disorder involves many organs and systems, including the skin, joints, kidneys, lungs, central nervous system, and blood-forming (hematopoietic) systems.

Dysregulated immune system along with the production of antibodies targeting self-antigens due to over activation of lymphocyte and autoantibody production is the causal factor for the development of this disease. Environmental factors such as toxic chemicals, genetic linkage, immune and inflammatory influences, hormonal, and certain medicines are found to be responsible for the prognosis of SLE [1-3].

Paediatric systemic lupus Erythematosus, Bullous Systemic Lupus Erythematosus (BSLE), SLE during Pregnancy are some variance of SLE having their own characteristic expressions at certain life stages as well [4 to 6].

Genetics of SLE:

Genetic linkage is implicated due to risk factors involving at least gene 183 loci including monogenic routes, more common in childhood onset SLE. Later occurrences are more frequent through polygenic and environmental routes [7].

Heterogeneity as well as intricate underlying pathogenesis interferes with development of lupus treatment in therapeutics. In addition, gut microbiota composition contributes to the disparity in phenotypic manifestations. For example,

intestinal commensal *Enterococcus gallinarum* can translocate to the liver and cause autoimmune hepatitis in patients with SLE [8].

Personalised treatment modality depending on the individual patient's disease severity and disease manifestations is in vogue. Glucocorticoids and unselective immunosuppressors have been administered to lessen the intensity of the disease till now. Under such circumstances, alternative therapies through multiple pathways are essential to treat the suffering patients.

Mechanism of action of gut microbiota

The mighty gut microbiota composition is found to have a strong influence on immunity, molecular mimicry, microbiota translocation, and epigenetic regulation are a few to mention.

Indigestible carbohydrates constitute a major type of dietary fiber which selects fiber-degrading bacteria that has the capability to produce short-chain fatty acids (SCFAs), beneficial to gut health under normal conditions playing a crucial role in maintaining homeostasis [9]. In a pilot clinical trial, increased production of SCFAs in the gut, significant enrichment of SCFAs-producing bacterial taxa, and reduction of inflammation-related bacterial taxa was observed after FMT treatment in patients [1;10]

Pathogenesis of gut microbiota dysbiosis in autoimmune diseases has been positively implicated with high-salt diet. In turn, a recent randomized controlled trial demonstrated that a low-salt diet increased circulating SCFAs and decreased blood pressures by affecting the gut microbiota in humans. Conclusion could be drawn that reduced dietary salt intake or targeting salt-sensitive associated protein could possibly be a promising therapeutic strategy in future [8].

Sequence similarity between foreign (peptides from microorganisms) and self peptides (the host's antigens) contribute to the expression of molecular mimicry. Some microbial antigens have the capability to trigger autoimmunity in hosts with genetic susceptibility to autoimmunity.

Bacterial antigens inducing antibodies can recognize self-antigens and contribute to the development of autoimmune diseases in humans. The best example is *Burkholderia* spp causes lupus symptoms due to molecular mimicry. In SLE pathogenesis by molecular mimicry such several signatures have been endorsed earlier [1;11]. Partial purified antigen of *Burkholderia* and transcriptional regulatory peptide RAGTDEGFG could bind to dsDNA antibodies in sera from patients with SLE suggesting that the

production antibodies in patients with SLE is associated with *Burkholderia* bacterial molecular mimicry.

The phenomena of molecular mimicry offer an explanation for the production of autoantibodies by different bacterial infections in SLE. For example, recent studies showed that peptides produced by *Odoribacter splanchnicus* and *Akkermansia muciniphila* bacteria are highly similar to Sm antigen and Fas antigen epitopes. In addition, these peptides from these bacteria can activate CD4+ T cells or B cells to produce autoantibodies is a significant observation [12]. Profound influence of environmental factors over the host genetics in shaping the human gut microbiota has been documented from the data from 1,046 healthy individuals [13].

In the recent past leaky gut has been a focus of interest for the scientific community as well as clinicians in therapeutics since, leaky gut has been implicated with intestinal barrier dysfunction as a causal factor for many diseases. Literature survey gives volumes of studies evidence to suggest that the impaired intestinal barrier may be one of the essential prerequisite factors responsible for the aggravation as well as progression of the disease. Increase in the intestinal translocation of endotoxins or other organic molecules, promote apoptosis and the leaky gut is one of the causal factors for the prognosis of many diseases that have been suggested earlier [14 to 19]. Consistent increase in IgG and a higher level of calprotectin in the faecal sample of SLE patients demonstrate impaired gut barrier function in these patients [20]. Similarly liver biopsy samples from both lupus patients and autoimmune hepatitis patients had *E. gallinarum* [21].

In addition, leaky gut and intestinal oxidative stress has been linked closely because of translocation of symbiotic bacteria or their contents out of the intestinal lumen. As a result, increase in the production of autoantibodies through molecular mimicry as well as deposition of immune complexes aggravating SLE progression has been anticipated. Unequivocal evidences for the presence of certain components in bacterial biofilms such as curli and curli-DNA complexes cross-reacting with autoantigens and induce the production of autoantibodies, resulting in SLE pathogenesis or disease aggravation was also demonstrated [22]. Pan *et al*., [22] has discussed the specific pathogenic infections of the gut such as *Enterococcus gallinarum (E. gallinarum*) and *Ruminococcus gnavus* (*R. Gnavus)* are of great significance to study the mechanism of action in patients. *E. gallinarum* could be very easily translocated into systemic organs by disrupting the intestinal barrier promoting Th17 and Tfh cell proliferation and autoantibody production in addition to directly inducing autoantigens, ERV proteins, and other substances to promote autoimmune processes. In spite of the influence of *R. gnavus* in the disease progression in SLE, the causal relationship remains still as an enigma.

Women between the ages of 15 and 44 are more prone to the disease than men and the ratio remains to be 1:10, though gender and age are no bar for the development of SLE. Influence of gut microbiota on estrogen, which could be implicated to promote type I interferon response and autoantibody production to aggravate SLE progression has been correlated. Androgen was found to play a negative role. Conclusion could be drawn that estrogen may account for gender bias in gut microbiota dysbiosis [23;24] though the underlying mechanism remains to be clarified [22].

SLE managed by FMT

The diversity and richness of gut microbiota was observed to decrease compared with healthy controls especially in patients with high SLE disease activity. Currently, however, the enigma is whether changes in the gut microbiota occurred after the onset of lupus disease and whether gut microbiota dysbiosis is the cause or consequence of SLE. The development of co-evolution to form a reciprocal relationship between microbiota and host immunity in a complex, dynamic, and context-dependent manner resulted due to a prolonged association between host and gut microbiota. This led to the advantage of reconstructing gut microbiota and normalizing the development of the immune system and immune response as well [25].

Short-term antibiotics exposure (following 1 week after antibiotics exposure) had a negative effect on these SLE patients due the aggravation of the severity of expression of the disease mainlydue to the depletion of beneficial gut microbiota such as Lactobacillus and *Bifidobacterium*, and simultaneously enriching harmful gut microbiota for lupus, such as *Klebsiella* and *Proteus*. This negative effect of the short-term antibiotic's exposure was confirmed from an experimental set up where 9 to 13 weeks old of MRL/lpr mice short-term antibiotics or FMT before the onset inhibited the therapeutic efficiency of prednisone on lupus. Inference could be drawn from this observation that gut microbiota before onset is important for lupus severity, progression and treatment [2]. Zhang et al., [2020] observed the influence of antibiotics to deplete *Firmicutes* and *Bacteroidetes* but a significant increase in *Proteobacteria* and *Verrucomicrobia* at phylum level. A significant observation was that at the genus level, antibiotics significantly down regulated 17 genera, including *Bifidobacterium*, *Bacteroides*, and *Lactobacillus*, and only two genera (*Klebsiella* and *Proteus*) were upregulated by antibiotics. FMT could restore the abundance of alpha diversity as well as abundances of Firmicutes and Bacteroidetes. In addition, 10 genera changed by antibiotics, such as *Bifidobacterium*, Adlercreutzia, *Bacteroides*, *Klebsiella*, and *Proteus*. Weakening the therapeutic efficiency of prednisone might be due to the decreases in the abundance of *Allobaculum*, *Bifidobacterium*, and *Adlercreutzia*, which were all negatively correlated with lupus activity and reported to be capable of immunoregulatory in the intestines. These vital observations are significant in therapeutics since gut microbiota could play a direct role in treating SLE or an auxiliary role in improving the efficiency of drugs on lupus [2]. A significant increase of *Lactobacillus reuteri* in both SLE patients and recipient mice is anticipated to be translocated from gut to the peripheral organs resulting in systemic immune activation leading to driving autoimmunity in a Toll-like receptor 7-dependent mouse model of SLE [26].

In mice model, Mu *et al.* [27] reported a significant reduction of *Lactobacillus* and supplementation with a mixture of Lactobacillus strains (*L.oris, L.rhamnosus, L.reuteri, L.johnsonii, and L. gasseri*) reversed leaky gut, contributed to an anti-inflammatory intestinal environment, and the survival value also was elevated [27]. In murine lupus model also, similar result was observed where depletion of *Lactobacillus* simultaneously increased *Lachnospiraceae* [28; 29]. In a healthy human intestine *Ruminococcus gnavus* (of the family Lachnnospiraceae), a symbiont, was significantly different between the groups of recipient mice model. In mice that received SLE faecal microbiota *R. gnavus* species showed a modest enrichment but *R. gnavus* density was noticed in patients with lupus nephritis [10, 30]. Azzouz *et al.*, [20] also observed earlier R. *gnavus* 5-fold greater abundant in SLE patients compared to healthy controls and correlated directly with SLE disease activity [20]. In SLE patients, evidence is available for the altered histidine significantly in GF mice treated with SLE patient faeces, as compared to those which received healthy faecal transplants.

Huang, C. *et al*., [10] performed a single-arm pilot clinical trial enrolling 24 patients with active SLE, of whom 20 received a full dose of FMT treatment to explore and ascertain the efficacy and safety for 12 weeks. A promising result was observed since a significant enrichment of SCFAs-producing bacterial taxa, reduction of inflammation-related bacterial taxa, increased production of SCFAs in the gut and reduced levels of IL-6 and CD4+ memory/naïve ratio in the peripheral blood was noticed. This was the first signature on the efficacy of the FMT in treatment modality of the patients.

Several studies have confirmed that gut microbiota dysbiosis in SLE, is associated with the reduced intestinal microbial diversity and the decreased *Firmicutes/Bacteroidetes* ratio [1, 20, 26]. After FMT, at week 4 *Firmicutes* significantly increased while simultaneously decreasing, *Bacteroidetes* resulting in the increased ratio of *Firmicutes* to *Bacteroidetes gradually* over the time and proved to be an advantage to the patients. To their surprise most of the significantly abundant taxa in post-FMT samples belonged to the phylum *Firmicutes*, including *Eubacterium hallii group*, *Dorea*, *Marvinbryantia*, and *Papillibacter*, belonging to SCFA-producing genera. Other enriched taxa in post-FMT samples

included *Porphyromonas*, *Pseudomonas* genera and *Alpha proteobacteria* class. Stool samples analysis from 117 untreated patients with SLE had a pro-inflammatory and autoimmune profile compared to healthy controls probably responsible for the prognosis of the disease [31]. Hevia *et al.* [28], observed in their study that in Spain a significantly lower F/B ratio in SLE patients (median ratio: 1.97) than in healthy subjects (median ratio: 4.86; $p < 0.002$). Significantly, *Firmicutes* are inversely correlated with the SLE disease activity index (SLEDAI score). Conclusion could draw that *Firmicutes* are having the capability to delay lupus progression as well as reduced F/B ratio, a significant observation in therapeutics.

Marian *et al*. [32], demonstrated for the first time from their pilot study in Egyptian SLE patients that the low ratio of Firmicutes/Bacteroidetes (F/B) ratio in SLE patients compared to healthy subjects was found to be ethnicity independent. This study also demonstrated a significant alteration in the faecal microbiota profile in recently diagnosed treatment-naive SLE Egyptian patients with lowering in both Firmicutes/Bacteroidetes ratio and *Lactobacillus* abundance compared to healthy controls which was negatively correlated to disease activity [32].

Genera *Streptococcus*, *Campylobacter*, and *Veillonella* were found to be positively associated with lupus activity. On the other hand, *Bifidobacterium* was negatively correlated with disease activity notably. The genera *Prevotella* and *Veillonella*, as well as the *Burkholderiales* order, were associated with increased systemic inflammation abundant in pre-FMT samples, but decreased after FMT is of therapeutic value in treating the patients. 42.12% of patients reached the SRI-4 primary outcome by week 12 when clinical observation ended. Clinical observations show the limited diversity of certain taxa of gut bacteria through FMT to SLE patients may give a promising result to restore a healthy repertoire of intestinal microbiota. This pilot trial provides sufficient evidence for a randomized, double-blind, placebo-controlled, multicentre clinical study to evaluate the long-term safety and effectiveness of FMT and to standardize the treatment modality [33].

Huang *et al.* [9] identified a combination of 14 important species in the baseline faecal microbiota, achieving good identification accuracy in distinguishing SRI-4 responders from non-responders (AUC: 0.89, 95% CI:0.74–1), with a sensitivity of 0.875 and a specificity of 0.8. In this regard, higher intestinal levels of *Anaerobutyricumhallii*, and lower abundance of unclassified *Lachnospiraceae*, unclassified *Parabacteroides and Senegalimassilia* stood out as most differentiating microbes at baseline between responders and non- responders. In addition, a significantly increased abundance of Bifidobacterium compared with the baseline, which may play dominant roles in FMT therapy. Further their indication for the presence of specific bacterial taxa in post-FMT gut microbiota is closely related to clinical response of FMT, with the presence of *Bifidobacterium longum*, *Bifidobacterium bifidum*, *Bifidobacterium breve* and unclassified *Bifidobacterium* is of significant therapeutic benefit. In addition, during the post –FMT elevated the amount of SCFAs including acetic acid, butyric acid, valeric acid, isovaleric acid, hexanoic acid, octanoic acid, and heptanoic acid, while reducing the amount of nonanoic acid and decanoic acid a benefit to the patients [9]. Azzouz *et al.* (2019) reported a5-fold greater abundance of *R. gnavus* in SLE patients compared to healthy controls and correlated directly with SLE disease activity [20].

Xin, Y et al., [1] observed efficacy results turned out to be 42.12% of the subjects who reached the primary endpoint SLE Responder Index-4 (SRI-4) from a total of 20 patients who were enrolled and accepted 3 doses of administration [1].16S rRNA gene sequencing analysis gave a legitimate evidence that FMT regimen increased the gut microbiota abundance significantly as well as the *Firmicutes/Bacteroidota* ratio, suggesting the ability of FMT to rectify the dysbiosis in patients supporting the observation of Ma *et al*.,[26]. Inference could be drawn that some special species may play a significant role in the pathogenesis of SLE though earlier observations has shown that gut microbiota in SLE patients showed significantly different compared with healthy cohorts. Firmicutes-to-Bacteroidetes ratio may be reduced or not significantly different and the diversity index of microbial communities are reduced in SLE [26].

Zheng, *et al*. [25] performed a Single-cell RNA sequencing and observed that the main cell types changed in SLE patients before and after FMT treatment. This study also revealed that lymphocytes altered in SLE following FMT treatment when peripheral blood mononuclear cells (PBMCs) were subjected to Single-cell RNA sequencing, a vital information for clinicians as well as scientific community working on SLE. Specific microbiota or their metabolites in FMT is responsible for the changes in immune cells need to be understood from further indepth investigation.

A meta-analysis including 11 case-control studies conducted in five countries and nine cities performed by Xiang et al. [36], observed the increased abundance of members from families *Enterobacteriaceae* and *Enterococcaceae* and decreased abundance of *Ruminococcaceae* in the gut microbiota of patients with SLE. Furthermore, a two-sample mendelian randomization study gave evidence that that *Actinobacteria, Bacillales*, *Coprobacter* and *Lachnospira are* inversely correlated with the risk of SLE, and *Bacilli*, *Eggertella* and *Lactobacillales* might be the risk factors for the development of SLE. More importantly, the result of this study gave a clue for the causal effects of gut microbiota on SLE [36].Ciccia and Gandolfo [34] and Xiang et al., [35] gave supportive evidence from their study that FMT appears to be a safe, feasible and potentially effective treatment modality in SLE.

Conclusion:

FMT significantly ameliorates disease in lupus by restoring the intestinal bacterial balance and intestinal barrier function in SLE. Donor stool screening must be improved to prevent infectious events to standardize FMT as a treatment modality. An interesting observation is that FMT early in the onset of lupus, suppresses the progression of lupus, but, at the same time, affects the therapeutic effect of glucocorticoid therapy. It is the responsibility of the clinicians to be careful if patients with SLE are routinely treated with glucocorticoids. There is a long way to go, but we are confident to set FMT as a new therapeutic option for SLE and look forward to the results of the ongoing in-depth study on the altered gut microbiota and its behaviour in the disease. However, in the present scenario evidence from studies show that limited diversity of certain gut bacterial taxa has been identified. Transfer of intestinal microbiota from healthy hosts to SLE patients may represent a promising approach to restore a healthy repertoire of intestinal microbiota.

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