Front. Med. 2022, 16(5): 686−700
https://doi.org/10.1007/s11684-022-0957-7

REVIEW

Recent advances in systemic lupus erythematosus and microbiota: from bench to bedside

Yijing Zhan[1], Qianmei Liu[1], Bo Zhang[1], Xin Huang (✉)[2], Qianjin Lu (✉)[1]

[1]Key Laboratory of Basic and Translational Research on Immune-Mediated Skin Diseases, Chinese Academy of Medical Sciences, Jiangsu Key Laboratory of Molecular Biology for Skin Diseases and STIs, Institute of Dermatology, Chinese Academy of Medical Sciences and Peking Union Medical College, Nanjing 210042, China; [2]Department of Dermatology, The Second Xiangya Hospital of Central South University, Institute of Dermatology and Venereology of Central South University, Hunan Clinical Medicine Research Center for Major Skin Diseases and Skin Health, Changsha 410011, China

Abstract **Systemic lupus erythematosus (SLE) is a complicated autoimmune disease affecting multiple systems and organs. It is highly heterogeneous, and it preferentially affects women at childbearing age, causing worldwide social burden. The pathogenesis of SLE mostly involves genetic predisposition, epigenetic dysregulation, overactivation of the immune system, and environment factors. Human microbiome, which is mostly composed of microbiota colonized in the gut, skin, and oral cavity, provides a natural microbiome barrier against environmental risks. The past decade of research has demonstrated a strong association between microbiota and metabolic diseases or gastrointestinal diseases. However, the role of microbiota in autoimmunity remains largely unknown until recently, when the technological and methodological progress facilitates further microbiota research in SLE. In this review, the latest research about the role and mechanisms of microbiota in SLE and the advances in the development of diagnostic and therapeutic strategies based on microbiota for SLE were summarized.**

Keywords systemic lupus erythematosus; microbiota; biotherapy

Introduction

Systemic lupus erythematosus (SLE) is a complicated and heterogeneous systemic autoimmune disease that preferentially affects women of childbearing age. It involves multiple systems and organs, including the kidney, skin, gastrointestinal tract, and joints [1]. Even though the precise pathogenesis of SLE remains incompletely understood, the occurrence and development of SLE is generally recognized to be a complex interplay among genetic, epigenetic, immune, environmental, and hormonal factors [2]. Several critical mechanisms have been implicated in the pathogenesis of SLE, such as overactivation of interferon-gamma (IFN-γ) pathway, polymorphic FcγRIIB, and overactivation of pathogenic T and B cells [3–6]. Epigenetic modifications, mostly including DNA methylation, histone modification, and miRNAs, have also been implicated in the overactivation of immune systems in lupus [7]. According to recent works, microbiota-derived metabolite promotes histone deacetylase 3 (HDAC3) activity in the gut, such as butyrate [8], and epigenetic alterations derived from differential microbiome compositions may be an additional connection between SLE and gut microbiota [9]. Although autoimmune diseases have traditionally been considered independent from the microbiota, the accumulating evidence during the past 10 years suggest that the immune-mediated diseases were related with the host microbiota [10,11]. The microbiota of the gut, skin, and oral cavity interrelate with the immune system once triggered by environmental factors and thus involved in the pathogenesis of autoimmune diseases, including SLE [12].

One of the most challenging aspects of SLE management is its unpredictable disease course and flare-remission patterns. SLE could cause lethal damage, such as renal failure, if not treated promptly. Early diagnosis and appropriate treatment are critical for the management of SLE [13]. With the unveiled connection between microbiota and autoimmunity, some novel diagnostic

Received: January 6, 2022; accepted: August 18, 2022

Correspondence: Qianjin Lu, qianlu5860@pumcderm.cams.cn;
Xin Huang, xin_huang@csu.edu.cn

tools and therapeutic strategies have been established recently [14–16]. The microbiota compositions and functional characteristics and the dynamic patterns of dysbiosis have been shown to be early signs of SLE flare. Rebuilding the microbiota may be a promising strategy for controlling SLE progression [17]. In the present review, the contribution and mechanisms of microbiota to SLE occurrence and pathogenesis and the diagnostic and therapeutic value of microbiota in SLE were summarized.

Role of microbiota in SLE

With the rapid development of next-generation sequencing (NGS) technology, the understanding of microbiome evolved at a striking speed. The human microbial diversity is characterized by the number and abundance of distinct types of microbial species. In 2012, the Human Microbiome Project Consortium conducted the largest cohort of microbiota in different body habitats. They found that even healthy individuals differ significantly in the microbiota of five major body areas, including the intestinal tract, skin, oral cavity, nasal cavity, and vagina [18]. The human microbiota is practically composed of four bacteria phyla (Proteobacteria, Actinobacteria, Firmicutes, and Bacteroidetes) and tends to be stable after 3 years old. These four phyla accounted for average 97.2% (± 2.9%) of skin microbiota, 98.4% (± 1.6%) of oral microbiota, and 96.4% (± 5.7%) of gut microbiota [18,19]. The diversity of microbiota not only comes from some of the most well-known factors, such as diet, environment, ethnic/racial background, and microbial exposure, but also multiple undetermined factors. In the past decades, the connection between microbiota and autoimmune diseases, including inflammatory bowel disease, SLE, and rheumatoid arthritis [20], has been revealed. The composition of mice and humans with lupus has been identified by high-throughput sequencing [21]. Interestingly, the relative abundance of certain bacterial strains, such as *Lactobacillus*, or the ratio of possible gut pathobionts has been implicated in the autoimmune responses in lupus (Table 1). Demonstrating the distribution of microbe in different body niches could help understand the pathogenesis of SLE more comprehensively.

Gut microbiota

The gut microbiota, which contains more than 2000 species of bacteria, is the largest component of the human microbiome ecosystem [22]. By metabolizing carbohydrates and protein, the gut microbiota provides nutrition and energy to host and affects key aspects of host development, fecundity, and even lifespan [23]. The role of the gut microbiota in SLE was first discovered by Apperloo Renkema *et al.* in 1994 [24]. They found that the quality of colonization resistance of gut microbiota in patients with active SLE was lower than that in healthy individuals, and the lower colonization resistance could lead to increased translocation of foreign bacteria, giving rise to the production of anti-dsDNA autoantibodies in SLE. Patients with inactive SLE had a lower abundance of Firmicutes and lower Firmicutes/Bacteroidetes (F/B) ratio than healthy controls (HCs) [25]. The decrease in Firmicutes was also observed in autoimmune diseases, such as type I diabetes (T1DM) [26,27] and rheumatoid arthritis [28]. The amount of Synergistetes was prone to decrease when the anti-dsDNA autoantibodies increased [29]. In addition, Synergistetes showed a strong positive correlation with the F/B ratio in HCs and a negative correlation with the serum levels of IL-6 and Th17 in patients with SLE.

The human gut microbiota has specific geographical features, and this is partially independent of races. For example, the gut microbiota of patients with SLE in Heilongjiang Province in Northeast China differed from that of Southern China and foreign countries [25,30–32]. The phylum Proteobacteria of patients with SLE in Heilongjiang Province in Northeast China increased, but this phenomenon was not seen in Spain and Southern China [25,30–32]. In Egypt, the gut microbiota showed a depletion of *Lactobacillus* abundance in patients newly diagnosed with SLE [32]. Decreased Ruminococcaceae and Lachnospiraceae and enriched Prevotellaceae and Bacteroidaceae in the gut were found in Spanish patients with SLE [25]. The intestinal *Actinomycetes* in these patients significantly increased [33].

In spite of individual differences, the gut microbiota of patients with SLE has many common features, such as lower F/B ratio and the negative correlation between the F/B ratio and Systemic Lupus Disease Activity Index (SLEDAI). Bacterial species could have different individual bacterial patterns, including the genera *Odoribacter* and *Blauti* and the family Rikenellaceae [34]. The distinct patterns of gut microbiota dysbiosis was notably correlated with disease activity. Gregg Silverman *et al.* reported that patients with SLE had an overall fivefold greater representation of *Ruminococcus gnavus*. They further discovered that anti-*R. gnavus* antibodies were the highest in classes III and IV active lupus nephritis, both of which have worse outcome than different lupus nephritis [35].

The association of gut microbiota alternation with the SLE disease activity was expanded; SLE disease activity was positively correlated with the abundance of the species *anginosus* and *dispar* and the genera *Streptococcus*, *Veillonella*, and *Campylobacter* while negatively correlated with the genus *Bifidobacterium* [36]. Estrogen state and X chromosome inactivation are

Table 1 Microbiota alternation in patients with SLE

Human subjects (*n*)	Region	Colonization site	Bacteria in SLE	Reference
SLE (20) vs. HC (20)	Spain	Gut	Phyla: Firmicutes/Bacteroidetes ratio ↓; Firmicutes ↓	[25]
SLE (20) vs. HC (20)	Spain	Gut	Phyla: Firmicutes/Bacteroidetes ratio, Synergistetes ↓	[29]
SLE (16) vs. HC (14)	China	Gut	Phyla: Proteobacteria ↑ Family: Enterobacterlaceae ↑; Ruminococcaceae, Prevotellaceae, Clostridiales ↓	[30]
SLE (45) vs. HC (48)	China	Gut	Phyla: Bacteroidetes, Actinobacteria, Proteobacteria ↑; Firmicutes/Bacteroidetes ratio, Firmicutes ↓ Genus: *Rhodococcus*, *Eggerthella*, *Klebsiella*, *Prevotella*, *Eubacterium*, *Flavonifractor* ↑; *Dialister*, *Pseudobutyrivibrio* ↓	[31]
SLE (20) vs. HC (20)	Egypt	Gut	Phyla: Firmicutes/Bacteroidetes ↓ Genus: *Lactobacillus* ↓	[32]
SLE (32) vs. HC (26)	China	Gut	Phyla: Bifidobacterium, Firmicutes/Bacteroidetes ratio↓; Enterobacteriaceae ↑ Family: Sartiphaea,Plavococcus ↓; Veillonella, Enterococci ↑ Genus: *Sartiphaea*, *Plavococcus* ↓; *Enterococcus*, *Veillonella* ↑	[33]
SLE (14) vs. HC (17)	USA	Gut	Gram-negative bacteria ↑ Phyla: Firmicutes/Bacteroidetes ratio was not different; Rikenellaceae, Proteobacteria ↑ Genus: *Odoribacter* ↓, *Blautia* ↑	[34]
SLE (61) vs. HC (17)	USA	Gut	Species: *Ruminococcus gnavus* ↑	[35]
SLE (40) vs. HC (22)	China	Gut	Genus: *Streptococcus*, *Campylobacter*, *Veillonella* ↑; Bifidobacterium ↓ Species: *Streptococcus anginosus* , *Veillonella dispar* ↑	[36]
SLE-G (17) vs. SLE + G (20) + HC (20)	China	Gut	Phyla: Bacteroidetes↓; Firmicutes/Bacteroidetes ratio ↑	[40]
SLE (33) vs. HC (28)	China	Gut	Phyla: Proteobacteria↑ Family: Ruminococcaceae, Christensenellaceae, Akkermansiaceae, Ruminococcaceae↓; Enterobacteriaceae↑ Genus: *Gammaproteobacteria*, *Bacilli*, *Escherichia*, *Shigella*, *Lachnoclostridium*, *Kluyvera* ↑; *Agathobacter*, *Ruminococcus*, *Coprococcus*, *Dialister*, *Faecalibacterium*, and *Subdoligranulum* ↓ Species: *Ruminococcus gnavus*↑; *Eubacterium coprostanoligenes*↓	[41]
SLE (21) vs. HC (25)	Spain	Gut	Phyla: Firmicutes/Bacteroidetes ratio ↓	[44]
SLE (21) vs. HC (21)	Spain	Gut	Phyla: The serum malondialdehyde was inverse correlations with *Cyanobacteria* and *Firmicutes* and positive with *Actinobacteria*; the C reactive protein was positive association with Lentisphaerae, Proteobacteria, and Verrucomicrobia	[45]
SLE (27) vs. HC (27)	Australia	Gut	Family: Coriobacteriaceae, Enterobacteriaceae ↑ Genus: *Bifidobacterium*, *Ruminiclostridium*, *Streptococcus*, *Collinsella* ↑; *Lachnoclostridium*, *Lachnospira*, and *Sutterella* ↓	[47]
SLE (47) vs. HC (203)	Japan	Gut	Species: *Streptococcus intermedius*, *Streptococcus anginosus* ↑	[48]
SLE (117) vs. HC (115)	China	Gut	Genus: *Desulfovibrio* ↓; *Blautia* ↑ Species: *Clostridium* species ATCC BAA-442, *Atopobium rimae*, *Shuttleworthia satelles*, *Actinomyces massiliensis*, *Bacteroides fragilis*, *Clostridium leptum* ↑	[49]
SLE (30) vs. HC (965)	Netherlands	Gut	Phyla: Firmicutes/Bacteroidetes ratio ↓; Bacteroidetes, Proteobacteria ↑ Genus: *Bacteroides*, *Alistipes* ↑ Species: *Bacteroides vulgatus*, *Bacteroides uniformis*, *Bacteroides ovatus*, *Bacteroides thetaiotaomicron* ↑	[57]
SLE (35) vs. HC (35)	China	Gut	Family: Ruminococcaceae ↓ Genus: *Lactobacillus*, *Prevotella*, *Blautia*, *Ruminococcus* ↑; *Bifidobacterium* ↓ Species: *Lactobacillus iners* ↑; *Bifidobacterium adolescentis*, *Bifidobacterium longum* ↓	[64]
SLE (16) vs. HC (11)	USA	Gut	Phyla: Firmicutes/Bacteroidetes ratio ↓	[71]
SLE (12) vs. HC (22)	USA	Gut	Species: *Lactobacillus* spp. ↑	[72]
SLE (92) vs. HC (217)	China	Gut	Phyla: Bacteroidetes, Proteobacteria, and Actinobacteria ↑; Firmicutes ↓ Family: Bacteroidaceae, Streptococcaceae ↑; Ruminococcaceae, Veillonellaceae, Lachnospiraceae ↓ Genus: *Ruminococcus*, *Klebsiella*, *Erysipelotrichaceae* ↑; *Faecalibacterium* ↓	[73]
SLE (69) vs. HC (49)	China	Skin	Phyla: Firmicutes, Acidobacteria, Gemmatimonadetes, and Tenericutes ↑ Genus: *Corynebacterium*, *Staphylococcus*, *Rothia*, *Actinomyces*, *Deinococcus* ↑; *Prevotella*, *Cutibacterium*, *Rhodococcus*, *Klebsiella* ↓ Species: *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus hominis* ↑; *Klebsiella pneumoniae*, *Rhodococcus erythropolis*, *Erwinia mallotivora*↓	[12]

(*Continued*)

Human subjects (*n*)	Region	Colonization site	Bacteria in SLE	Reference
SLE (20) vs. HC (20)	China	Skin	Phyla: Firmicutes, Bacteroidetes, Spirochaetae, Verrucomicrobia, Tenericutes↑; Actinobacteria and Armatimonadetes ↓ Class: Alphaproteobacteria ↓ Order: Sphingomonadales ↓ Family: Acetobacteraceae, Sphingomonadaceae, Phyllobacteriaceae ↓; Christensenellaceae, Erysipelotrichaceae, Methylocystaceae, Burkholderiaceae, and Verrucomicrobiaceae↑ Genus: *Nevskia*, *Stenotrophomonas*, *Phyllobacterium*, *Novosphingobium* ↓; *Barnesiella*, *Acinetobacter* ↑ Species: *Chryseobacterium taiwanense*, *Nevskia aquatilis* ↓; *Corynebacterium matruchotii*, *Ruminococcus* sp. 5_1_39BFAA ↑ Compared with non-rash region of SLE, genus in the rash region: *Halomonas* ↑*; Pelagibacterium, Novosphingobium, Curvibacter* ↓	[56]
SLE (117) vs. HC (115)	China	Oral	Species: *Clostridium* species ATCC BAA-442, *Atopobium rimae*, *Shuttleworthia satelles*, *Actinomyces massiliensis*, *Bacteroides fragilis*, *Clostridium leptum* ↑	[49]
SLE (30) vs. HC (965)	Netherlands	Oral	Genus: *Actinomyces* ↓; *Lactobacillu* ↑	[57]
Anti-Ro$^+$ mothers of neonatal lupus children (25) vs. HC (7)	USA	Oral	Phyla: Proteobacteria ↓; Actinobacteria, Firmicutes, Bacteroidetes ↑ Class: Coriobacteriia, Bacilli, Negativicutes↑; Betaproteobacteria ↓ Order: Neisseriale ↓ Family: Neisseriaceae ↓ Genus: *Streptococcus*, *Veillonella* ↑; *Neisseria* ↓	[59]
SLE (52) vs. HC (52)	Brazil	Oral	Genus: *Fretibacterium*, *Selenomonas* ↑ Species: *Prevotella nigrescens* ↑	[60]
SLE-A (31) vs. SLE-I (29) + HC (31)	USA	Oral	Species in SLE-A: *Treponema denticola*, *Tannerella forsythia* ↑; *Capnocytophaga gingivalis*, *Streptococcus gordonii*, *Prevotella nigrescens*, *Capnocytophaga ochracea*, *Fusobacterium nucleatum*, *Streptococcus sanguinis* ↓	[61]
SLE (35) vs. HC (35)	China	Oral	Genus: *Streptococcus*↓; *Prevotella*, *Selenomonas*, *Veillonella* ↑ Species: *Streptococcus anginosus* ↓	[64]

HC, healthy control; vs., versus; SLE-A, active SLE; SLE-I, inactive SLE; SLE + G, patients having undergone glucocorticoid treatment; SLE-G, patients without undergone glucocorticoid treatment.

important risk factors for female predisposition of lupus [37]. Pregnancy and lactation may interfere with the autoimmune response via regulation of gut microbiota [38]. The composition and diversity of gut microbiota significantly changed in pregnant and breastfeeding MRL/lpr mice. Even the same alternation of gut microbiota could result in different disease outcomes between pregnant and breastfeeding and naive MRL/lpr mice. A possible mechanism is that their responses to *Lactobacillus animalis* or antibiotics were different from those of normal mice, and it had nothing to do with microbial translocation. Other possible mechanisms included different regulations of Treg cells, indoleamine 2,3-dioxygenase, and IFN-γ.

Given the fact that antibiotics, which remove gut bacteria, could trigger lupus flares [39], the traditional treatments for SLE, including corticosteroid and immunosuppressants, influence the diversity and structure of gut microbiota. The analysis of the difference in gut microbiota composition of patients with SLE with or without glucocorticoid treatment (SLE + G or SLE − G) has shown that the gut microbiota of HC and SLE + G cohort had decreased Bacteroidetes level and higher ratio F/B [40].

Shotgun sequencing and metagenomic analyses showed that not only the microorganism species but also the genes and genomes of the microbiota and its products influence the host environment. Diverse metabolic pathways were found in patients with SLE during different disease processes [36]. 16S rRNA sequencing and gas chromatography–mass spectrometry analysis of the gut microbiota and metabolites of pediatric patients with SLE showed that the increased *Sphingomonas* of Proteobacteria was correlated with protein digestion and absorption. A decrease in the abundance of healthy periodontal point of patients with SLE compared with that of HC indicated that the oral bacteria may spread to the gut [41]. Microbial metabolites as signals of microbiota could activate or inhibit endogenous signal pathways *in vivo*, including short-chain fatty acids (SCFAs), tryptophan, and lipoprotein metabolism [42,43]. Patients with SLE exhibited decreased gut microbial biodiversity; remarkably reduced N-acetylmuramic acid and homoserine lactone; and significantly increased levels of ribose-1,5-bisphosphate, serum levels of free fatty acids, and fecal SCFAs. The patients with SLE could not be classified based on their body mass index, whereas healthy controls could. Metabolic impairment

was also found to be a frequent hallmark of SLE [44]. Free fatty acids are produced when oils and fats are hydrolyzed. Free fatty acids and antioxidant alteration are important mediators for anti-inflammatory responses, and their abnormality is closely related to immune disorder [45]. The results showed serum C reactive protein had a positive association with Verrucomicrobia, Proteobacteria, and Lentisphaerae in feces, and the serum levels of malondialdehyde displayed negative correlation with Cyanobacteria and Firmicutes and positive correlation with Actinobacteria. The overgrowth of *Enterococcus gallinarum*, a typical gut commensal bacterium, was related to increased intestinal epithelial permeability, and translocation of *E. gallinarum* could trigger the onset of SLE [46]. In the lamina propria of the small intestine, *E. gallisepticum* induced an increase in plasmacytoid dendritic cells (pDCs) that produce IFN-α. *E. gallinarum* also produced aryl hydrocarbon receptor (AhR) ligand, which could enhance the activation and differentiation of Th17 and follicular helper T (Tfh) cells. In liver, *E. gallinarum* induced the expression of lupus-specific autoantigens and inflammatory factors and thus enhanced the pathogenic deposition of immune complexes in multiple organs. Meanwhile, metabolomic signatures have been investigated in Sjögren's syndrome and primary anti-phospholipid syndrome, and similar alterations of *E. gallinarum* and its metabolomic profiles were found in these autoimmune diseases [47].

In a metagenome-wide association study, the abundance of *Streptococcus anginosus* and *Streptococcus intermedius* and the *Streptococcus*-derived genes in gut microbiome was found to be increased in Japanese patients with SLE. Seven biological pathways, such as sulfur metabolism and flagellar assembly, were significantly enriched, showing that the increase in *Streptococcus*-derived genes, including the altered redox reaction, was related to the pathology of SLE [48]. The species composition and functional distribution of the gut microbiota also differed between patients with SLE and HC. *Atopobium rimae*, *Clostridium* sp. ATCC BAA-442, *Actinomyces massiliensis*, *Shuttleworthia satelles*, *Bacteroides fragilis*, and *Clostridium leptum* were significantly enriched in SLE but reduced after treatment [49]. In general, the difference in function was more significant than the difference in species composition. Other metabolic pathways involved in SLE include the synthesis of branched-chain amino acids, thiamine (vitamin B1), lipopolysaccharide, and the degradation of inositol.

The damage of multi-organs caused by immune-complex deposition has been a suspending problem for the long-term management of SLE. Substantial research advances have been achieved in the involvement of gut microbiota in the organ-specific damage of SLE [50]. Cardiovascular disease is the most common comorbidity of SLE. *Lactobacillus* protected patients from important risk factors of cardiovascular disease, including hypertension and endothelial dysfunction [51]. In a germ-free or germ-depleted mouse model, hypertension and vascular complications were found after transplantation of the gut microbiota of patients with SLE, but no excessive autoimmunity, endotoxemia, and renal inflammation were observed [52]. In addition, an increase in the proportion of *Bacteroides* was associated with hypertension, and Th17 infiltration in the vascular system induced by the gut microbiota may be the cause of vascular damage and hypertension by *Bacteroides*.

Skin microbiota

Skin provides a crucial barrier against external pathogens. Microbiota is generally accepted to be an important guard of skin health. Skin microorganisms interact between many hosts, and they are sensitive to environmental stimuli. They are also closely affected by the cutaneous and mucosal immune system [53]. Skin microbiota interacts with mammalian host cells through symbiotic or symbiotic interactions to prevent the colonization and infection of opportunistic or pathogenic organisms, maintain defense and immune tolerance, and promote tissue repair and barrier functions [54]. Approximately 80% of patients with SLE have cutaneous involvement, and 25% of patients with SLE showed skin lesion as the first symptom [55]. However, very little research was reported on the skin microbiota of patients with SLE. The existing research showed that the skin microbiota of patients with SLE was related to their clinical features, including gender, renal involvement, serum low complement level, and myositis [12]. Disordered skin microbiota of patients with SLE was reported in a study involving 69 patients with SLE, 20 patients with dermatomyositis, and 49 HCs. It is manifested as elevated proportions of *Staphylococcus* and *Corynebacterium* and decreased relative abundance of *Cutibacterium* in the lesioned skin. Further research on the skin microbiota in the rash and non-rash areas of 20 patients with SLE showed that the rash area had decreased *Novosphingobium*, *Pelagibacterium*, and *Curvibacte* and increased *Halomonas* compared with the non-rash area [56]. Large-scale, multi-cohort and multifactor studies are needed for deeper association analysis of SLE and the skin microbiome in the future.

Oral microbiota

Many autoimmune diseases have oral mucosa involvements. Patients with SLE often have oral manifestations, such as xerostomia, insufficient saliva

secretion, unspecified oral ulcers, and increased periodontal disease. Primary Sjögren's syndrome is an autoimmune disease characterized by the focal infiltration of inflammatory lymphocytes in exocrine glands, causing dry eyes and dry mouth. Primary Sjögren's syndrome and patients with SLE had significantly different oral microbiota compositions, but they share similar changes in the composition of gut microbiota [57]: reduced bacterial richness and F/B ratio and increased *Bacteroides* species. Neonatal lupus cohort research demonstrated that in mothers with anti-Ro^+ antibodies, their kids had a significant risk of developing clinicopathological autoimmunity, including Sjögren's syndrome, SLE, and undifferentiated autoimmune disease [58]. The microbial diversity at all levels from the kingdom to the species in saliva of anti-Ro^+ mothers decreased [49]. Interestingly, some oral microbiome was enriched in the gut of patients with SLE, including *A. massiliensis*, *S. satelles*, and *A. rimae*, which are closely related to oral inflammation, implicating that the bacteria enriched in the gut of patients with SLE may have originated from oral cavity. Indeed, the overall transmission rate of salivary microorganisms to the intestinal tract of patients with SLE increased [49].

The subgingival microflora imbalance of SLE was related with periodontal status [56,59,60]. A 1.76-fold increase in the risk of periodontal disease was observed in patients with SLE [60]. The abundance of *Prevotella nigrescens*, *Prevotella oulorum*, *Prevotella oris*, *Selenomonas noxia*, Lachnospiraceae, and *Leptotrichia* in the periodontal inflammation site and periodontal healthy site in patients with SLE with periodontitis increased [59], whereas the bacteria related to periodontal health decreased. Recent research found that the abundance of most serious oral pathogens (*Tannerella forsythia* and *Treponema denticola*) increased in the periodontal area of patients with active SLE compared with patients with inactive SLE and HC [61]. In addition, the presence of pathogenic bacteria was positively related with the level of systemic inflammation, as evidenced by the elevated concentrations of IL-6, IL-17, and IL-33 in patients with SLE with periodontitis [59,62]. Restoration of the imbalanced oral ecosystem by periodontal therapy improved the response of patients with SLE to conventional treatments and reduced the disease activity [63].

However, a notable detail that the microbiome compositions in feces and saliva are not always consistent. For example, in a small sample study of 35 patients with SLE, 16S rRNA gene sequencing showed a decrease in bacterial abundance and diversity in the feces of patients with SLE, while the bacterial diversity in saliva increased [64]. Certain specific oral microbiota patterns have been found in patients with different organ targeted SLE. For example, a deficiency of *Bifidobacteria* has been observed in patients with SLE with arthritis. Their dominant saliva bacteria *Streptococcus*, *Veillonella*, *Prevotella*, and *Bacteroides* were negatively correlated with the SLEDAI of patients [65].

The local oral microenvironment is involved in the development of SLE. Oral lesions could cause systemic involvement through the production of circulating autoantibodies against oral microorganisms [49]. As a result of the interrupted oral barrier, viral infections related to the pathogenesis of SLE (i.e., EBV and CMV) may also appear in the oral cavity and affect the onset of disease. These findings highlighted the link between the oral microbiota and SLE, indicating that the reduction in oral inflammation could promote a less pathogenic oral microbial spectrum. In addition to the intestine, the oral cavity may represent the origin of the dormant blood microbiome associated with chronic inflammatory diseases (including SLE) [66].

In summary, the development of SLE and the organ involvement of SLE were related to the dysbiosis of microbiota (Table 1). Microbiome changes observed in SLE include a decrease in the ratio of bacteria, such as Gram-positive Firmicutes to Gram-negative Bacteroidetes, and an overabundance or depletion of certain species, including *Lactobacillus*. Similar changes were observed in other autoimmune diseases, indicating the potential of intervention at microbiota levels in treating autoimmune diseases. Atherosclerosis and cardiovascular events are comorbidities for SLE. Microbiota could affect SLE onset by influencing endocrine metabolism and endothelial function (Fig. 1).

Potential mechanisms of action of microbiota in SLE

Microbiota dysbiosis and leaky gut

The so called "intestinal barrier" includes anatomy barrier (surface mucus and epithelial layer), microbiota barrier, and immune barrier. The interruptions of microbiome homeostasis in the gut could lead to increased paracellular transport, apoptosis, or transcellular permeability, thus causing a "leaky gut." Even though the cause and mechanism of "leaky gut" in SLE are still unclear, some researchers suggested that the skin–gut axis may be one mechanism [67]. The skin–gut axis may contribute to cutaneous autoimmunity, which also appears to be biologically relevant in SLE.

Compared with female HC, the overall increase in secreted IgA was more than twice in 61 female patients with lupus, demonstrating mucosal immune activation in patients with lupus [35]. Fecal calprotectin is well acknowledged to be the biomarker of barrier defects and intestinal inflammation in patients with inflammatory

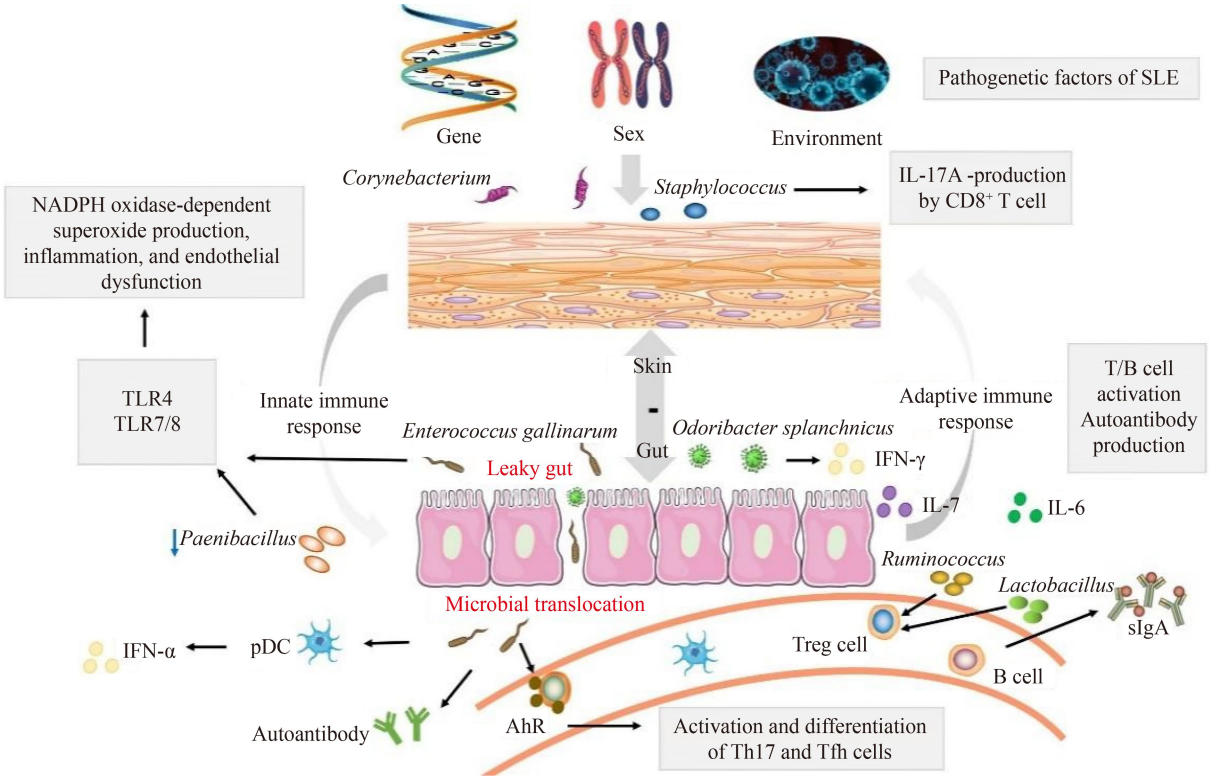

Fig. 1 Role of skin–gut axis in SLE. The host skin and gut microbiota are linked via metabolic pathways. Genetic, environment, and hormonal factors affect the composition of skin and gut microbiota through the innate and adaptive immune responses. The activation of TLR7/8 was induced by specific gut bacteria, such as *Enterococcus gallisepticum*. The translocation of *E. gallisepticum* resulted in the activation of the aryl hydrocarbon receptor (AhR) system, which enhanced the activation and differentiation of Th17 and follicular helper T (Tfh) cells and autoantibody production. In the lamina propria of the small intestine, *E. gallisepticum* could also induce an increase in pDCs that produce IFN-α. In addition, reduction in *Paenibacillus* genus may lead to elevated lipopolysaccharide and increased expression of TLR4 in the vasculature, leading to increased NADPH oxidase-dependent superoxide production, inflammation, and endothelial dysfunction. Along with the activation of the innate immune response, bacteria such as *Odoribacter splanchnicus* could activate the adaptive immune response by increasing the secretion of IFN-γ and IL-17A. The proportion of *Ruminococcus* and *Lactobacillus* was positively correlated with the absolute count of Treg lymphocytes. When T and B cells are overactivated, autoantibodies such as ANA and dsDNA are produced, and high-avidity IgA (sIgA) is secreted. The immune complex deposited on skin, intestine, and other organs and inflammatory cytokines, such as IL-17, IFN-γ, and IL-6, were released, resulting in organ damage. The relationship between skin microbiota and SLE remains to be elusive, even though studies have shown that certain bacteria strains, such as *Staphylococcus* and *Corynebacterium*, increased in the skin of patients with SLE. Some research showed that superficial colonization of *Staphylococcus epidermidis* may induce the elevation of IL17A producing $CD8^+$ T cell. SLE, systemic lupus erythematosus; TLR7/8, Toll-like receptor 7/8; Th17, T helper 17; IFN-α, interferon-α; pDC, plasmacytoid dendritic cells; IFN-γ, interferon-γ; IL-17A, interleukin-17A; IL-6, interleukin-6.

bowel disease (IBD). Notably, leaky gut barrier resulted in fecal calprotectin elevation and chronic endotoxin exposure in the immune systems in patients with SLE [35,68]. The serum soluble CD14 and a1-acid glycoprotein levels in patients with lupus without original intestinal diseases significantly increased, which has been confirmed to be attributed to intestinal bacterial translocation [69]. *R. gnavus*-specific lipoglycan was proposed as a novel immunodominant antigen and an innate stimulator of TLR2 binding in SLE [35]. In summary, patients with lupus suffer from impaired intestinal barrier integrity, causing the translocation of symbionts or their components. However, unlike patients with IBD, they usually do not suffer from obvious enteritis.

Molecular mimicry

The molecular mimicry is another possible mechanism for how microbiota contributes to SLE pathogenesis. Some commensal bacteria colonizing the gut, skin, or oral cavity share epitope with Ro60 autoantigen. Anti-Ro60 appears in 50% of patients with SLE. It was the most common and earliest preclinical anti-nuclear antibody in SLE. Martin A. Kriegel *et al.* found that commensal Ro60 orthologues could trigger autoimmunity through cross-reactivity in human. SLE CD4 memory T cell specific to Ro60 autoantigen could be reactivated by bacteria with Ro60 orthologues. No significant different bacterial operational taxonomic units were found in the gut, skin, or oral microbiomes between anti-Ro60 antibody-positive

and anti-Ro60 antibody-negative subjects, indicating that this autoimmune response was not depending on the change in microbiota composition. Therefore, anti-Ro60 is a functional link between the gut, skin, or oral microbiota with a primordial autoimmune response in humans [70]. Some other genera, such as *Fretibacterium*, Lachnospiraceae, *Prevotella*, and *Selenomonas*, also participated in SLE through their orthologues cross-activating with autoantibodies, providing further evidence for molecular mimicry hypothesis [51,71]. *L. reuteri* was translocated to internal organs, and single *L. reuteri* could aggravate systemic autoimmunity in GF and SPF conditions [72]. The peptide "YLYDGRIFI" from *Odoribacter splanchnicus* was similar to the human peptide "ILQDGRIFI" antigen presented to T cells. This peptide could increase the secretion of IFN-γ and IL-17A. Moreover, the peptide "DGQFCM" from *Akkermansia muciniphila* was mimicked with the "DGQFCH" of the human extracellular part, which could specifically bind to IgG produced by memory B cells in a subgroup of patients with SLE. Compared with patients with untreated SLE or those with SLE after treatment, the IFN-γ and IL-17A secretion from the PBMC of patients with anti-Sm-positive SLE increased. The *O. splanchnicus* of patients with SLE was not enriched and reduced after treatment. *A. muciniphila* exerted immunopathogenic functions in SLE as it was positively correlated with all characteristics of inflammation in patients with SLE, including blood IgA, IgM, and erythrocyte sedimentation rate [49]. In conclusion, the peptides produced by *O. splanchnicus* and *A. muciniphila* were highly similar to the epitopes of the SLE characteristic autoantigens Sm and Fas and thus could activate $CD4^+$ T and B cells and participate in the occurrence and development of SLE.

Microbiome and pathogen interaction with immune system

The overactivation of T cells, excessive production of a large pool of autoantibodies, and deposition of autoantibodies or immune complex are critical for SLE onset. Innate immunity and acquired immunity are involved in this process. The microbiome flora participates in the induction, education, and function maturation of the host immune system. The homeostatic immunity to the microbiota is vital to the health of the host [73]. The microorganisms of the microbiota are basically tolerated by the immune system under steady-state conditions. Some bacteria and their structural components or bacterial metabolites may be able to pass through the intestinal epithelium and reach the blood or even organs. Regulatory T cells (Treg cells) help tolerate self-tissues and organs by inhibiting autoreactive T cells. Once the balance of Treg and other pathogenic immune cells are interrupted, pathogenic immune responses promote the release of inflammatory cytokines, giving rise to various pathological conditions [74]. The microbe–host interaction in the intestinal flora is mostly mediated by IgA and T cell responses [75].

The microbiota has effect in immune cell phenotype switching and functions in patients with SLE. Evidence has shown that the microbiota may affect T cell activation pathways and hormone levels, including the development of Treg, T helper type 1 (Th1), and Th2 cells in some autoimmune diseases [70,76,77]. The expression of IFN-γ, IL-2R, IL-10, IL-35, and TNF-α was slightly lower in patients with SLE treated with glucocorticoids and HC than in patients with untreated SLE, implicating that those cytokines are probably pathogenic in the disease course [40]. Moreover, women are more prone to SLE. The gut microbiota composition in a (SWR×NZB) F1 (SNF1) mouse model of spontaneous lupus was different between male and female mouse, and such difference was considered to significantly contribute to the pro-inflammatory immune phenotype and disease progression of female SNF1 mice [40].

The defects of the complement system are closely connected with lupus. Anti-*R. gnavus* antibodies were directly related to SLEDAI scores and anti-dsDNA antibody levels but negatively related to C3 and C4 [35]. Assuming that circulating immune cells may respond to bacterial dynamics in the intestine, a notable detail is that the proportion of *Ruminococcus* was positively correlated with the absolute count of Treg lymphocytes but not related with the number of Th1, Th2, and Th17 cells [74].

Apart from the adaptive immune response, the innate immune system is involved in the homeostasis of microecosystem. The innate immune system is modulated through TLR-7/8 and TLR4 activation. *E. gallisepticum* could translocate to liver and activate anti-dsDNA antibody production in genetically susceptible hosts through TLR-7/8 activation [46]. The abundance of Synergistetes in the intestine was negatively correlated with plasma anti-dsDNA antibody titers and IL-6 levels [78]. Bacterial lipopolysaccharide stimulates and increases the expression of TLR4 in the vasculature, leading to increased NADPH oxidase-dependent superoxide production, inflammation, and endothelial dysfunction [78]. Another study suggested that elevated plasma autoantibody and lipopolysaccharide may result from the reduction in *Paenibacillus* genus [79]. Therefore, the enhanced TLR4 activation may be related to the development and maintenance of SLE hypertension.

Potential diagnostic and therapeutic strategy based on microbiota for SLE

Diagnostic potential of microbiota

SLE is a highly heterogeneous disease with various

clinical manifestations, making the diagnosis difficult. Even though SLE has several classification criteria, such as the EULAR/ACR-2019 and SLICC-2012 criteria, those criteria still have caveats and could not be applied to all patients. As the recent studies found significant associations between the microbiota composition and SLE pathology, microbiota information could potentially provide reference for the diagnosis of SLE [80]. Several bacterial taxa were identified to be potential markers for cutaneous lupus erythematosus, especially *S. epidermidis* and *Staphylococcus aureus* [12]. Some oral microbiota was a biomarker of SLE, which may be associated with autoimmune response. The relative abundance of Proteobacteria and more specifically, class Betaproteobacteria, decreased with clinical severity of patients with SLE; the potential for cross-recognition oral microbiota and Ro60 indicated a possible role of *Lautropia mirabilis* as potentiator or inducer of SLE in anti-Ro^+ mothers [58]. Ji-Liang Li *et al.* used suitable random forest models for prediction of SLE activity (AUC = 0.811) and another random forest model that could identify SLE from HC and rheumatoid arthritis (AUC = 0.792) [36]. With the current mass data collected from 16S rRNA sequencing and high throughput sequencing in patients with SLE, the machine learning model based on initial gut microbiota may be the new trend for the development of diagnostic tools for SLE.

Treatment strategy based on microbiota

In the past decades, the invention of biologics changed the outcome of many rheumatology diseases. Even though several novel biologics for SLE are under development, very limited biologics have been proven to be successful in clinic.

Specific microbial clades may be a potential safe strategy for SLE therapeutic operations if used properly. The microbiome composition of the human body could be reshaped by dietary interventions, probiotics, prebiotics, and specially tailored antibiotics.

As for probiotics, most attempts are in the pre-clinical stage. Glucocorticoids were prone to cause alterations in the gut microbiota. Treatment with prednisone, a commonly used steroid for SLE, was associated with reduced *Rikenella*, *Mucispirillum*, *Bilophila*, and *Oscillospira* and increased *Anaerostipes* [81]. In preliminary experiments, the neonatal vaccination against *E. gallinarum* was considered a promising approach for controlling the autoimmunity properties driven by the microbiota [46]. The outgrowth of *Lactobacilli* and the concomitant decrease in Clostridiales have been detected in only a subset of patients with SLE, although they limited the intervention of such bacteria as a general therapy in SLE [72]. *L. reuteri* was generally known as a probiotic, but studies showed that the *L. reuteri* in the TLR7-dependent lupus model was enriched, transferable, and aggravated the incidence of lupus, driving lupus-related pathogenesis in the gnotobiotic mice. This phenomenon could be ameliorated by supplementing dietary resistant starch [72]. In summary, the above research suggested the potential of diet therapy in treating patients with SLE.

Multiple studies have found that depletion of gut *Bifidobacterium* and *Lactobacillus* of MRL/lpr mice accelerated lupus, and the oral gavage with these two bacterial supplementations had therapeutic effects in SLE (Table 2) [51,82–85]. Treatment with *Lactobacillus fermentum* CECT5716 ameliorated lupus activity, cardiac blood, pressure, splenomegaly, and renal hypertrophy and reduced the circulating pro-inflammatory cytokines of lupus mice [84]. Another research demonstrated that the *Bifidobacterium breve* CECT7263 and *L. fermentum* CECT5716 could reduce plasma ds-DNA antibody, T cell activation, and Th17 polarization in IMQ-treated group of SLE [83]. According to the research on the effectiveness of *L. reuteri* GMNL-263, *Lactobacillus paracasei* GMNL-32, and *L. reuteri* GMNL-89 in NZB/W F1 mice, oral gavage could mitigate hepatic inflammation and apoptosis in lupus-prone mice by reducing the expression levels of hepatic IL-1β, IL-6, and TNF-α proteins [84]. Moreover, the differentiation of $CD4^+CD25^+FoxP3^+$ Treg cells was significantly increased by supplementation with GMNL-263 [86]. Therefore, manipulation of gut microbiota is a promising approach to prevention of SLE.

Maryam Rastin *et al.* found that tolerogenic probiotics, such as *Lactobacillus delbrueckii* and *Lactobacillus rhamnosus*, may be a promising therapy of SLE [87–89]. They could promote monocytes to produce regulatory dendritic cells *in vitro*; the expression of indoleamine-2,3-dioxygenase and IL-10 increased and that of IL-12 decreased in tolerogenic probiotic-treated mature dendritic cells compared with treatment with lipopolysaccharide [87]. Th1, Th17, and inflammatory cytokines IL-6, IFN-γ, and IL-17 decreased after treatment with tolerogenic probiotics, which could delay SLE onset, thus playing a more prominent role in the prevention of SLE [88,89].

As gut-associated lymphoid tissue is composed of the largest component of the mucosal immune system, regulating the gut microbiota is considered as a plausible strategy for SLE treatment. Dietary intervention is the most common method to regulate the gut microbiota (Table 2). Cuervo *et al.* reported that the intake of apple and orange was directly associated with *Bifidobacterium* and *Lactobacillus* in SLE, respectively, and red wine caused the most significant variation of *Faecalibacterium* [90]. Another research indicated that mice who drank acidic pH water developed nephritis at a slower rate, and the neutral pH water-recipient mice carried relatively

Table 2 Application of microecological agents in the treatment of SLE *in vivo*

Microecological agents	Intervention	Models	Mode of administration	Effects	Reference
Probiotics	*Lactobacillus oris* (F0423), *Lactobacillus rhamnosus* (LMS201), *Lactobacillu reuteri* (CF48-3A), *Lactobacillu johnsonii* (135-1-CHN), and *Lactobacillu gasseri* (JV-V03)	MRL/lpr	Oral gavage, 3 W to dissection	"leaky gut," IL-6, IgG2a ↓; IL-10 ↑	[61]
	Lactobacillus fermentum CECT5716	NZB/W F1	Oral gavage, 15 W	B and T cell, lymphocytes, IL-17α, IFN-γ, TNF-α, IL-21 ↓	[84]
	Lactobacillus fermentum CECT5716 and/or *Bifidobacterium breve* CECT7263	Imiquimod-induced lupus model	Oral gavage, 8–16 W	SLE activity and vascular inflammation ↓	[85]
	Lactobacillus paracasei GMNL-32, *Lactobacillus reuteri* GMNL-89, and *Lactobacillus reuteri* GMNL-263	NZB/W F1	Oral gavage, 8–20 W	IL-1β, IL-6, and TNF-α ↓	[86]
	Lactobacillus reuteri GMNL-263	NZB/W F1	Oral gavage, 16–28 W	TUNEL-positive cells, Fas death receptor-related components, apoptosis ↓	[87]
	Lactobacillus delbrueckii PTCC 1743 and *Lactobacillus rhamnosus* ATCC 9595	Pristane-induced lupus model	Oral gavage, 2–6 M	Th17, Th1, CTL, IFN-γ, IL-17 ↓	[90]
	Lactobacillus delbrueckii and *Lactobacillus rhamnosus*	Pristane-induced lupus model	Oral gavage, 0–6 M	Tregs, Foxp3 ↑; lipogranuloma, ANA, anti-dsDNA, IL-6 ↓	[91]
Dietary deviations	Resistant starch	TLR7.1 Tg, TLR7 KO, and C57BL/6 mice	Oral gavage, 7 W	*Lactobacillus reuteri,* pDCs, interferon pathways, organ involvement, mortality ↓	[72]
	Regular diet	Patients with SLE (20) vs. HC (20)	Diet	Orange intake was directly associated with *Lactobacillus* and apple intake was associated with *Bifidobacterium* in SLE, whilst red wine was the best contributor to *Faecalibacterium* variation	[92]
	Autoclaved neutral pH (7.0–7.2) water vs. acidic pH (3.0–3.2) water	(SWR×NZB) F1	Oral gavage, to dissection	Simple dietary deviations, such as pH of drinking water, influenced lupus incidence and affected the composition of gut microbiome	[93]
	Low fiber vs. normal fiber	NZB/W F1 mice	Oral gavage, 4 W to dissection	Low fiber diet is related with overall survival ↓; CD44, IFN-γ, IL-10, Treg, effector Treg, Tfh ↑	[95]
Microbiota transplant	Fecal microbiota transplantation	C57BL/6J, TC (SLE mice)	Fecal gavage, once every other day for 10 days	ds-DNA antibody in germ free mice after FMT from SLE mice ↑	[100]
	Fecal microbiota transplantation	MRL/lpr	Oral gavage, 2 W antibiotics, 4W fecal suspensions	Lupus severity and progression ↓	[101]

HC, healthy control; W, weeks; M, months; IL-6, interleukin-6; IL-17α, interleukin-17α; IFN-γ, interferon-γ; TNF-α, tumor necrosis factor α; IL-21, interleukin-21; ANA, antinuclear antibody; IL-10, interleukin-10; pDCs, plasmacytoid dendritic cells; IFN-γ, interferon-γ; Tfh cell, follicular helper T cell.

higher levels of auto-antibodies and plasma cells, indicating that the pH of water significantly influenced the gut microbiota and disease pathogenesis in lupus [91]. Consistent with the above findings, probiotics triggered immune shifts, effectively reduced inflammation, and thus ameliorated the symptoms of SLE. The regulation of Th17 and Treg lymphocyte populations is a possible immunology mechanism for probiotic treatment.

Whole-diet plan could influence the composition and function of gut microbiota, including individual dietary components and food processing [92]. As known, low dietary fiber intake is an important lifestyle factor in Western countries. High-fiber diet promotes the growth of *Bifidobacterium* while inhibiting the growth of spoilage bacteria. High-fiber diet is also beneficial for metabolic diseases, such as obesity and diabetes, whereas low-fiber diet could increase SLE disease activity [93]. Overall, these studies proved that dietary deviations affect the composition of the gut microbiota and the onset of lupus.

Fecal microbiota transplant (FMT) is the most effective means to rebuild the gut microbiota (Table 2). It was

selected as one of the breakthrough medical advances in recent years [94–96]. So far, FMT has been applied to IBD, obesity, metabolic syndrome, depressive disorder, and many other diseases in clinic. Interestingly, after transplanting fecal microbiota in SLE mice to make the fecal microbiota of the recipient mice similar to that of their donors, the production of anti-dsDNA antibodies increased and certain lupus susceptibility genes of the germ-free mice significantly changed [97]. FMT by intragastric administration was used to treat severe SLE in a murine model, the decreased anti-dsDNA antibody titer after FMT indicated that the FMT with healthy donor had therapeutic effects on SLE [98,99]. This study indicated that harmful fecal microbiota promoted the inflammatory response in the pathogenesis of SLE and reshaping the gut microbiota by FMT provided alternatives for the treatment of refractory or severe SLE.

Donor selection and its microbiota management are critical for the success of FMT; determining the colonization rules and optimizing transplantation strategies after FMT implantation were a top priority [100]. Although the mechanism of successful FMT was still not fully resolved (after all, one stool does not fit all), the procedure may be more effective in combination with specific diets or dietary supplements in the treatment for SLE. In addition, the commensal skin microbiota transplant has been proposed as a potential therapy of skin disease. In a small proof-of-concept study, patients with skin diseases were transplanted with healthy volunteers' commensal bacteria for 16 weeks, and their skin symptoms improved by an average of 65%, along with a decrease in the use of topical steroid [101]. The *S. epidermidis* model is a common model for skin commensal bacteria. A recent breakthrough discovery came when a phase 1 randomized clinical trial showed that a single strain of *Staphylococcus*, *Staphylococcus hominis* A9 (*Sh*A9) isolated from healthy human skin, could be used for bacteriotherapy of atopic dermatitis. In this study, Richard Gallo and his colleagues isolated more than 8000 *Staphylococcus* from healthy donors and found that a bacterium called *Sh*A9 killed some *S. aureus* strains on the skin and inhibited the overall expression of *S. aureus* toxin. The local eczema severity was improved in participants with *S. aureus* directly killed by *Sh*A9 [102]. However, no clinical trial for skin microbiota transplant in lupus has been successful so far.

In conclusion, the biological therapy of SLE includes probiotics, dietary deviations, and FMT (Fig. 2). The above biological therapies could alleviate SLE through the regulation of microbiota and autoimmunity. Currently reported probiotics mainly include *Lactobacillus* and *Bifidobacterium*, and the dietary deviation is mostly coming from varied intake of fiber, wine, and fruit. FMT and miniFMT that selects specific intestinal strains for colonization appeared to be a promising therapy for lupus. Establishment of a complete technical system of the therapy and its effectiveness and safety need to be further confirmed, and its mechanism in the occurrence and development in SLE needs further study.

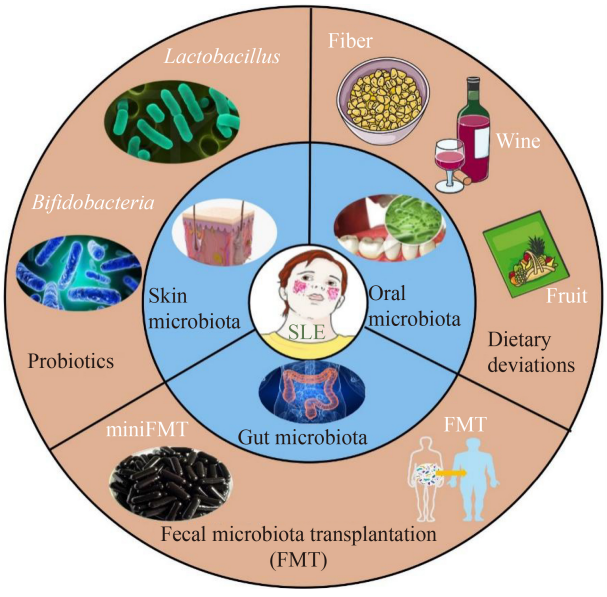

Fig. 2 Current microbial interventions and therapies in SLE. The dysbiosis of the gut, skin, and oral microbiota plays an important role in the occurrence and development of SLE. Biological therapies of SLE, including probiotics, dietary deviations, and fecal microbiota transplant (FMT) alleviated SLE through the regulation of microbiota. The currently reported probiotics mainly include *Lactobacillus* and *Bifidobacterium*, and the dietary deviations mainly include the intake of fiber, wine, and fruit. FMT and miniFMT that selects specific intestinal bacterial strains for colonization appeared to be a promising therapy for lupus.

Conclusions and future prospects

Recent research demonstrated the importance of microbiota in the development and occurrence of SLE. The impaired intestinal barrier function, molecular mimicry, and immunology disorders are implicated to trigger microbiota imbalance and influence SLE disease activity and organ involvements. The restricted gut, oral, and skin microbiota diversities were related with different microbiota-associated immune-dysregulatory features in SLE, and the microbial translocation and adaptive responses caused by the microbiota change could result in Th17 responses and autoantibody production. Moreover, the heterogeneity and remission-relapse course of SLE make it difficult to realize individualized care in the management of SLE. Given the fact that the microbiota composition of each individual is unique and the unveiled connection between host microbiota composition and SLE, the intervention of SLE-specific microbiomes may serve as an alternative for SLE treatment in the future.

The microbiota-based techniques used to regulate dysbiosis include probiotics, dietary deviations, and FMT. These therapies have potential advantages over traditional systemic therapies, such as glucocorticoid and immunosuppressants, as they cause less adverse events. Therefore, the mechanism and therapeutic potential of microbiota in SLE are worth investigating.

Acknowledgements

This work is supported by CAMS Innovation Fund for Medical Sciences (No. 2021-I2M-1-059) and the Non-profit Central Research Institute Fund of Chinese Academy of Medical Sciences (Nos. 2020-RC320-003 and 2021-RC320-001).

Compliance with ethics guidelines

Yijing Zhan, Qianmei Liu, Bo Zhang, Xin Huang, and Qianjin Lu declare that they have no conflicts of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

References

1. Tsokos GC. Systemic lupus erythematosus. N Engl J Med 2011; 365(22): 2110–2121
2. Dema B, Charles N. Autoantibodies in SLE: specificities, isotypes and receptors. Antibodies (Basel) 2016; 5(1): 2
3. Tsokos GC, Lo MS, Costa Reis P, Sullivan KE. New insights into the immunopathogenesis of systemic lupus erythematosus. Nat Rev Rheumatol 2016; 12(12): 716–730
4. Espéli M, Smith KG, Clatworthy MR. FcγRIIB and autoimmunity. Immunol Rev 2016; 269(1): 194–211
5. Honda K, Littman DR. The microbiota in adaptive immune homeostasis and disease. Nature 2016; 535(7610): 75–84
6. Fu R, Xia Y, Li M, Mao R, Guo C, Zhou M, Tan H, Liu M, Wang S, Yang N, Zhao J. Pim-1 as a therapeutic target in human lupus nephritis. Arthritis Rheumatol 2019; 71(8): 1308–1318
7. Singh S, Li SSL. Epigenetic effects of environmental chemicals bisphenol A and phthalates. Int J Mol Sci 2012; 13(8): 10143–10153
8. Wu SE, Hashimoto-Hill S, Woo V, Eshleman EM, Whitt J, Engleman L, Karns R, Denson LA, Haslam DB, Alenghat T. Microbiota-derived metabolite promotes HDAC3 activity in the gut. Nature 2020; 586(7827): 108–112
9. Sánchez B, Hevia A, González S, Margolles A. Interaction of intestinal microorganisms with the human host in the framework of autoimmune diseases. Front Immunol 2015; 6: 594
10. Gensollen T, Iyer SS, Kasper DL, Blumberg RS. How colonization by microbiota in early life shapes the immune system. Science 2016; 352(6285): 539–544
11. Bach JF. The hygiene hypothesis in autoimmunity: the role of pathogens and commensals. Nat Rev Immunol 2018; 18(2): 105–120
12. Huang C, Yi X, Long H, Zhang G, Wu H, Zhao M, Lu Q. Disordered cutaneous microbiota in systemic lupus erythematosus. J Autoimmun 2020; 108: 102391
13. Luo S, Long H, Lu Q. Recent advances in understanding pathogenesis and therapeutic strategies of systemic lupus erythematosus. Int Immunopharmacol 2020; 89 (Pt A): 107028
14. Biliouris K, Nestorov I, Naik H, Dai D, Xiao G, Wang Q, Pellerin A, Rabah D, Lesko LJ, Trame MN. A pre-clinical quantitative model predicts the pharmacokinetics/pharmacodynamics of an anti-BDCA2 monoclonal antibody in humans. J Pharmacokinet Pharmacodyn 2018; 45(6): 817–827
15. Markham A. Baricitinib: first global approval. Drugs 2017; 77(6): 697–704
16. Mathian A, Pha M, Haroche J, Cohen-Aubart F, Hié M, Pineton de Chambrun M, Boutin THD, Miyara M, Gorochov G, Yssel H, Cherin P, Devilliers H, Amoura Z. Withdrawal of low-dose prednisone in SLE patients with a clinically quiescent disease for more than 1 year: a randomised clinical trial. Ann Rheum Dis 2020; 79(3): 339–346
17. Rahbar Saadat Y, Hejazian M, Bastami M, Hosseinian Khatibi SM, Ardalan M, Zununi Vahed S. The role of microbiota in the pathogenesis of lupus: dose it impact lupus nephritis? Pharmacol Res 2019; 139: 191–198
18. Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. Nature 2012; 486(7402): 207–214
19. Andoh A. Physiological role of gut microbiota for maintaining human health. Digestion 2016; 93(3): 176–181
20. Choi SC, Brown J, Gong M, Ge Y, Zadeh M, Li W, Croker BP, Michailidis G, Garrett TJ, Mohamadzadeh M, Morel L. Gut microbiota dysbiosis and altered tryptophan catabolism contribute to autoimmunity in lupus-susceptible mice. Sci Transl Med 2020; 12(551): eaax2220
21. Zhang L, Qing P, Yang H, Wu Y, Liu Y, Luo Y. Gut microbiome and metabolites in systemic lupus erythematosus: link, mechanisms and intervention. Front Immunol 2021; 12: 686501
22. Neish AS. Microbes in gastrointestinal health and disease. Gastroenterology 2009; 136(1): 65–80
23. Heintz-Buschart A, Wilmes P. Human gut microbiome: function matters. Trends Microbiol 2018; 26(7): 563–574
24. Apperloo-Renkema HZ, Bootsma H, Mulder BI, Kallenberg CG, van der Waaij D. Host-microflora interaction in systemic lupus erythematosus (SLE): circulating antibodies to the indigenous bacteria of the intestinal tract. Epidemiol Infect 1995; 114(1): 133–141
25. Hevia A, Milani C, López P, Cuervo A, Arboleya S, Duranti S, Turroni F, González S, Suárez A, Gueimonde M, Ventura M, Sánchez B, Margolles A. Intestinal dysbiosis associated with systemic lupus erythematosus. MBio 2014; 5(5): e01548–14
26. Boerner BP, Sarvetnick NE. Type 1 diabetes: role of intestinal microbiome in humans and mice. Ann N Y Acad Sci 2011; 1243(1): 103–118
27. Brown CT, Davis-Richardson AG, Giongo A, Gano KA, Crabb DB, Mukherjee N, Casella G, Drew JC, Ilonen J, Knip M, Hyöty H, Veijola R, Simell T, Simell O, Neu J, Wasserfall CH, Schatz D, Atkinson MA, Triplett EW. Gut microbiome metagenomics analysis suggests a functional model for the development of autoimmunity for type 1 diabetes. PLoS One 2011; 6(10): e25792

28. Kasselman LJ, Vernice NA, DeLeon J, Reiss AB. The gut microbiome and elevated cardiovascular risk in obesity and autoimmunity. Atherosclerosis 2018; 271: 203–213
29. López P, de Paz B, Rodríguez-Carrio J, Hevia A, Sánchez B, Margolles A, Suárez A. Th17 responses and natural IgM antibodies are related to gut microbiota composition in systemic lupus erythematosus patients. Sci Rep 2016; 6(1): 24072
30. Wei F, Xu H, Yan C, Rong C, Liu B, Zhou H. Changes of intestinal flora in patients with systemic lupus erythematosus in northeast China. PLoS One 2019; 14(3): e0213063
31. He Z, Shao T, Li H, Xie Z, Wen C. Alterations of the gut microbiome in Chinese patients with systemic lupus erythematosus. Gut Pathog 2016; 8(1): 64
32. Gerges MA, Esmaeel NE, Makram WK, Sharaf DM, Gebriel MG. Altered profile of fecal microbiota in newly diagnosed systemic lupus erythematosus Egyptian patients. Int J Microbiol 2021; 2021: 9934533
33. Zhu WF. Alteration of gut microbiome in patients with systemic lupus erythematosus. Doctoral dissertation. Hangzhou: Zhejiang University, 2018 (in Chinese)
34. Luo XM, Edwards MR, Mu Q, Yu Y, Vieson MD, Reilly CM, Ahmed SA, Bankole AA. Gut microbiota in human systemic lupus erythematosus and a mouse model of lupus. Appl Environ Microbiol 2018; 84(4): e02288–17
35. Azzouz D, Omarbekova A, Heguy A, Schwudke D, Gisch N, Rovin BH, Caricchio R, Buyon JP, Alekseyenko AV, Silverman GJ. Lupus nephritis is linked to disease-activity associated expansions and immunity to a gut commensal. Ann Rheum Dis 2019; 78(7): 947–956
36. Li Y, Wang HF, Li X, Li HX, Zhang Q, Zhou HW, He Y, Li P, Fu C, Zhang XH, Qiu YR, Li JL. Disordered intestinal microbes are associated with the activity of systemic lupus erythematosus. Clin Sci (Lond) 2019; 133(7): 821–838
37. Lu Q, Wu A, Tesmer L, Ray D, Yousif N, Richardson B. Demethylation of CD40LG on the inactive X in T cells from women with lupus. J Immunol 2007; 179(9): 6352–6358
38. Mu Q, Cabana-Puig X, Mao J, Swartwout B, Abdelhamid L, Cecere TE, Wang H, Reilly CM, Luo XM. Pregnancy and lactation interfere with the response of autoimmunity to modulation of gut microbiota. Microbiome 2019; 7(1): 105
39. Mu Q, Zhang H, Luo XM. SLE: another autoimmune disorder influenced by microbes and diet? Front Immunol 2015; 6: 608
40. Guo M, Wang H, Xu S, Zhuang Y, An J, Su C, Xia Y, Chen J, Xu ZZ, Liu Q, Wang J, Dan Z, Chen K, Luan X, Liu Z, Liu K, Zhang F, Xia Y, Liu X. Alteration in gut microbiota is associated with dysregulation of cytokines and glucocorticoid therapy in systemic lupus erythematosus. Gut Microbes 2020; 11(6): 1758–1773
41. Wen M, Liu T, Zhao M, Dang X, Feng S, Ding X, Xu Z, Huang X, Lin Q, Xiang W, Li X, He X, He Q. Correlation analysis between gut microbiota and metabolites in children with systemic lupus erythematosus. J Immunol Res 2021; 2021: 5579608
42. Sonnenburg JL, Bäckhed F. Diet-microbiota interactions as moderators of human metabolism. Nature 2016; 535(7610): 56–64
43. Rojo D, Hevia A, Bargiela R, López P, Cuervo A, González S, Suárez A, Sánchez B, Martínez-Martínez M, Milani C, Ventura M, Barbas C, Moya A, Suárez A, Margolles A, Ferrer M. Ranking the impact of human health disorders on gut metabolism: systemic lupus erythematosus and obesity as study cases. Sci Rep 2015; 5(1): 8310
44. Rodríguez-Carrio J, López P, Sánchez B, González S, Gueimonde M, Margolles A, de Los Reyes-Gavilán CG, Suárez A. Intestinal dysbiosis is associated with altered short-chain fatty acids and serum-free fatty acids in systemic lupus erythematosus. Front Immunol 2017; 8: 23
45. González S, Gutie Rrez-Díaz I, Lo Pez P, Suárez A, Fernández-Navarro T, Sánchez B, Margolles A. Microbiota and oxidant-antioxidant balance in systemic lupus erythematosus. Nutr Hosp 2017; 34(4): 934–941
46. Manfredo Vieira S, Hiltensperger M, Kumar V, Zegarra-Ruiz D, Dehner C, Khan N, Costa FRC, Tiniakou E, Greiling T, Ruff W, Barbieri A, Kriegel C, Mehta SS, Knight JR, Jain D, Goodman AL, Kriegel MA. Translocation of a gut pathobiont drives autoimmunity in mice and humans. Science 2018; 359(6380): 1156–1161
47. Bellocchi C, Fernández-Ochoa Á, Montanelli G, Vigone B, Santaniello A, Quirantes-Piné R, Borrás-Linares I, Gerosa M, Artusi C, Gualtierotti R, Segura-Carrettero A, Alarcón-Riquelme ME, Beretta L. Identification of a shared microbiomic and metabolomic profile in systemic autoimmune diseases. J Clin Med 2019; 8(9): 1291
48. Tomofuji Y, Maeda Y, Oguro-Igashira E, Kishikawa T, Yamamoto K, Sonehara K, Motooka D, Matsumoto Y, Matsuoka H, Yoshimura M, Yagita M, Nii T, Ohshima S, Nakamura S, Inohara H, Takeda K, Kumanogoh A, Okada Y. Metagenome-wide association study revealed disease-specific landscape of the gut microbiome of systemic lupus erythematosus in Japanese. Ann Rheum Dis 2021; 80(12): 1575–1583
49. Chen BD, Jia XM, Xu JY, Zhao LD, Ji JY, Wu BX, Ma Y, Li H, Zuo XX, Pan WY, Wang XH, Ye S, Tsokos GC, Wang J, Zhang X. An autoimmunogenic and proinflammatory profile defined by the gut microbiota of patients with untreated systemic lupus erythematosus. Arthritis Rheumatol 2021; 73(2): 232–243
50. de la Visitación N, Robles-Vera I, Toral M, Duarte J. Protective effects of probiotic consumption in cardiovascular disease in systemic lupus erythematosus. Nutrients 2019; 11(11): 2676
51. Mu Q, Zhang H, Liao X, Lin K, Liu H, Edwards MR, Ahmed SA, Yuan R, Li L, Cecere TE, Branson DB, Kirby JL, Goswami P, Leeth CM, Read KA, Oestreich KJ, Vieson MD, Reilly CM, Luo XM. Control of lupus nephritis by changes of gut microbiota. Microbiome 2017; 5(1): 73
52. de la Visitación N, Robles-Vera I, Toral M, Gómez-Guzmán M, Sánchez M, Moleón J, González-Correa C, Martín-Morales N, O' Valle F, Jiménez R, Romero M, Duarte J. Gut microbiota contributes to the development of hypertension in a genetic mouse model of systemic lupus erythematosus. Br J Pharmacol 2021; 178(18): 3708–3729
53. Egert M, Simmering R, Riedel CU. The association of the skin microbiota with health, immunity, and disease. Clin Pharmacol Ther 2017; 102(1): 62–69
54. Flowers L, Grice EA. The skin microbiota: balancing risk and reward. Cell Host Microbe 2020; 28(2): 190–200
55. Ribero S, Sciascia S, Borradori L, Lipsker D. The cutaneous spectrum of lupus erythematosus. Clin Rev Allergy Immunol 2017; 53(3): 291–305
56. Zhou HY, Cao NW, Guo B, Chen WJ, Tao JH, Chu XJ, Meng X,

Zhang TX, Li BZ. Systemic lupus erythematosus patients have a distinct structural and functional skin microbiota compared with controls. Lupus 2021; 30(10): 1553–1564

57. van der Meulen TA, Harmsen HJM, Vila AV, Kurilshikov A, Liefers SC, Zhernakova A, Fu J, Wijmenga C, Weersma RK, de Leeuw K, Bootsma H, Spijkervet FKL, Vissink A, Kroese FGM. Shared gut, but distinct oral microbiota composition in primary Sjögren's syndrome and systemic lupus erythematosus. J Autoimmun 2019; 97: 77–87
58. Clancy RM, Marion MC, Ainsworth HC, Blaser MJ, Chang M, Howard TD, Izmirly PM, Lacher C, Masson M, Robins K, Buyon JP, Langefeld CD. Salivary dysbiosis and the clinical spectrum in anti-Ro positive mothers of children with neonatal lupus. J Autoimmun 2020; 107: 102354
59. Corrêa JD, Calderaro DC, Ferreira GA, Mendonça SM, Fernandes GR, Xiao E, Teixeira AL, Leys EJ, Graves DT, Silva TA. Subgingival microbiota dysbiosis in systemic lupus erythematosus: association with periodontal status. Microbiome 2017; 5(1): 34
60. Rutter-Locher Z, Smith TO, Giles I, Sofat N. Association between systemic lupus erythematosus and periodontitis: a systematic review and meta-analysis. Front Immunol 2017; 8: 1295
61. Pessoa L, Aleti G, Choudhury S, Nguyen D, Yaskell T, Zhang Y, Li W, Nelson KE, Neto LLS, Sant'Ana ACP, Freire M. Host-microbial interactions in systemic lupus erythematosus and periodontitis. Front Immunol 2019; 10: 2602
62. Marques CP, Victor EC, Franco MM, Fernandes JM, Maor Y, de Andrade MS, Rodrigues VP, Benatti BB. Salivary levels of inflammatory cytokines and their association to periodontal disease in systemic lupus erythematosus patients. A case-control study. Cytokine 2016; 85: 165–170
63. Fabbri C, Fuller R, Bonfá E, Guedes LK, D'Alleva PS, Borba EF. Periodontitis treatment improves systemic lupus erythematosus response to immunosuppressive therapy. Clin Rheumatol 2014; 33(4): 505–509
64. Liu F, Ren T, Li X, Zhai Q, Xu X, Zhang N, Jiang P, Niu Y, Lv L, Shi G, Feng N. Distinct microbiomes of gut and saliva in patients with systemic lupus erythematous and clinical associations. Front Immunol 2021; 12: 626217
65. Li BZ, Zhou HY, Guo B, Chen WJ, Tao JH, Cao NW, Chu XJ, Meng X. Dysbiosis of oral microbiota is associated with systemic lupus erythematosus. Arch Oral Biol 2020; 113: 104708
66. Potgieter M, Bester J, Kell DB, Pretorius E. The dormant blood microbiome in chronic, inflammatory diseases. FEMS Microbiol Rev 2015; 39(4): 567–591
67. Kiyohara H, Sujino T, Teratani T, Miyamoto K, Arai MM, Nomura E, Harada Y, Aoki R, Koda Y, Mikami Y, Mizuno S, Naganuma M, Hisamatsu T, Kanai T. Toll-like receptor 7 agonist-induced dermatitis causes severe dextran sulfate sodium colitis by altering the gut microbiome and immune cells. Cell Mol Gastroenterol Hepatol 2019; 7(1): 135–156
68. Shi L, Zhang Z, Yu AM, Wang W, Wei Z, Akhter E, Maurer K, Costa Reis P, Song L, Petri M, Sullivan KE. The SLE transcriptome exhibits evidence of chronic endotoxin exposure and has widespread dysregulation of non-coding and coding RNAs. PLoS One 2014; 9(5): e93846
69. Fotis L, Shaikh N, Baszis KW, Samson CM, Lev-Tzion R, French AR, Tarr PI. Serologic evidence of gut-driven systemic inflammation in juvenile idiopathic arthritis. J Rheumatol 2017; 44(11): 1624–1631
70. Greiling TM, Dehner C, Chen X, Hughes K, Iñiguez AJ, Boccitto M, Ruiz DZ, Renfroe SC, Vieira SM, Ruff WE, Sim S, Kriegel C, Glanternik J, Chen X, Girardi M, Degnan P, Costenbader KH, Goodman AL, Wolin SL, Kriegel MA. Commensal orthologs of the human autoantigen Ro60 as triggers of autoimmunity in lupus. Sci Transl Med 2018; 10(434): eaan2306
71. Corrêa JD, Calderaro DC, Ferreira GA, Mendonça SM, Fernandes GR, Xiao E, Teixeira AL, Leys EJ, Graves DT, Silva TA. Subgingival microbiota dysbiosis in systemic lupus erythematosus: association with periodontal status. Microbiome 2017; 5(1): 34
72. Zegarra-Ruiz DF, El Beidaq A, Iñiguez AJ, Lubrano Di Ricco M, Manfredo Vieira S, Ruff WE, Mubiru D, Fine RL, Sterpka J, Greiling TM, Dehner C, Kriegel MA. A diet-sensitive commensal lactobacillus strain mediates TLR7-dependent systemic autoimmunity. Cell Host Microbe 2019; 25(1): 113–127.e6
73. Ruff WE, Greiling TM, Kriegel MA. Host-microbiota interactions in immune-mediated diseases. Nat Rev Microbiol 2020; 18(9): 521–538
74. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. Cell 2014; 157(1): 121–141
75. Zhang S, Wang J, Chen J, Zhang M, Zhang Y, Hu F, Lv Z, Gao C, Li Y, Li X. The level of peripheral regulatory T cells is linked to changes in gut commensal microflora in patients with systemic lupus erythematosus. Ann Rheum Dis 2021; 80(11): e177
76. Naik S, Bouladoux N, Linehan JL, Han SJ, Harrison OJ, Wilhelm C, Conlan S, Himmelfarb S, Byrd AL, Deming C, Quinones M, Brenchley JM, Kong HH, Tussiwand R, Murphy KM, Merad M, Segre JA, Belkaid Y. Commensal-dendritic-cell interaction specifies a unique protective skin immune signature. Nature 2015; 520(7545): 104–108
77. Coit P, Sawalha AH. The human microbiome in rheumatic autoimmune diseases: a comprehensive review. Clin Immunol 2016; 170: 70–79
78. Katz-Agranov N, Zandman-Goddard G. The microbiome and systemic lupus erythematosus. Immunol Res 2017; 65(2): 432–437
79. Toral M, Gómez-Guzmán M, Jiménez R, Romero M, Sánchez M, Utrilla MP, Garrido-Mesa N, Rodríguez-Cabezas ME, Olivares M, Gálvez J, Duarte J. The probiotic *Lactobacillus coryniformis* CECT5711 reduces the vascular pro-oxidant and pro-inflammatory status in obese mice. Clin Sci (Lond) 2014; 127(1): 33–45
80. Zhao Y, Zhang B, Liu C, Ren G. Method for accurate diagnose of lupus erythematosus skin lesions based on microbial rDNA sequencing. Saudi J Biol Sci 2020; 27(8): 2111–2115
81. He Z, Kong X, Shao T, Zhang Y, Wen C. Alterations of the gut microbiota associated with promoting efficacy of prednisone by bromofuranone in MRL/lpr mice. Front Microbiol 2019; 10: 978
82. Toral M, Robles-Vera I, Romero M, de la Visitación N, Sánchez M, O'Valle F, Rodriguez-Nogales A, Gálvez J, Duarte J, Jiménez R. *Lactobacillus fermentum* CECT5716: a novel alternative for the prevention of vascular disorders in a mouse model of systemic lupus erythematosus. FASEB J 2019; 33(9): 10005–10018
83. de la Visitación N, Robles-Vera I, Moleón-Moya J, Sánchez M,

Jiménez R, Gómez-Guzmán M, González-Correa C, Olivares M, Toral M, Romero M, Duarte J. Probiotics prevent hypertension in a murine model of systemic lupus erythematosus induced by Toll-like receptor 7 activation. Nutrients 2021; 13(8): 2669

84. Hsu TC, Huang CY, Liu CH, Hsu KC, Chen YH, Tzang BS. *Lactobacillus paracasei* GMNL-32, *Lactobacillus reuteri* GMNL-89 and *L. reuteri* GMNL-263 ameliorate hepatic injuries in lupus-prone mice.. Br J Nutr 2017; 117(8): 1066–1074
85. Yeh YL, Lu MC, Tsai BC, Tzang BS, Cheng SM, Zhang X, Yang LY, Mahalakshmi B, Kuo WW, Xiang P, Huang CY. Heat-killed *Lactobacillus reuteri* GMNL-263 inhibits systemic lupus erythematosus-induced cardiomyopathy in NZB/W F1 mice. Probiotics Antimicrob Proteins 2021; 13(1): 51–59
86. Tzang BS, Liu CH, Hsu KC, Chen YH, Huang CY, Hsu TC. Effects of oral *Lactobacillus administration* on antioxidant activities and $CD4^+CD25^+$forkhead box P3 $(FoxP3)^+$ T cells in NZB/W F1 mice. Br J Nutr 2017; 118(5): 333–342
87. Esmaeili SA, Mahmoudi M, Rezaieyazdi Z, Sahebari M, Tabasi N, Sahebkar A, Rastin M. Generation of tolerogenic dendritic cells using *Lactobacillus rhamnosus* and *Lactobacillus delbrueckii* as tolerogenic probiotics. J Cell Biochem 2018; 119(9): 7865–7872
88. Mardani F, Mahmoudi M, Esmaeili SA, Khorasani S, Tabasi N, Rastin M. *In vivo* study: Th1-Th17 reduction in pristane-induced systemic lupus erythematosus mice after treatment with tolerogenic *Lactobacillus* probiotics. J Cell Physiol 2019; 234(1): 642–649
89. Khorasani S, Mahmoudi M, Kalantari MR, Lavi Arab F, Esmaeili SA, Mardani F, Tabasi N, Rastin M. Amelioration of regulatory T cells by *Lactobacillus delbrueckii* and *Lactobacillus rhamnosus* in pristane-induced lupus mice model. J Cell Physiol 2019; 234(6): 9778–9786
90. Cuervo A, Hevia A, López P, Suárez A, Sánchez B, Margolles A, González S. Association of polyphenols from oranges and apples with specific intestinal microorganisms in systemic lupus erythematosus patients. Nutrients 2015; 7(2): 1301–1317
91. Johnson BM, Gaudreau MC, Al-Gadban MM, Gudi R, Vasu C. Impact of dietary deviation on disease progression and gut microbiome composition in lupus-prone SNF1 mice. Clin Exp Immunol 2015; 181(2): 323–337
92. Wolter M, Grant ET, Boudaud M, Steimle A, Pereira GV, Martens EC, Desai MS. Leveraging diet to engineer the gut microbiome. Nat Rev Gastroenterol Hepatol 2021; 18(12): 885–902
93. Schäfer AL, Eichhorst A, Hentze C, Kraemer AN, Amend A, Sprenger DTL, Fluhr C, Finzel S, Daniel C, Salzer U, Rizzi M, Voll RE, Chevalier N. Low dietary fiber intake links development of obesity and lupus pathogenesis. Front Immunol 2021; 12: 696810
94. Mocanu V, Zhang Z, Deehan EC, Kao DH, Hotte N, Karmali S, Birch DW, Samarasinghe KK, Walter J, Madsen KL. Fecal microbial transplantation and fiber supplementation in patients with severe obesity and metabolic syndrome: a randomized double-blind, placebo-controlled phase 2 trial. Nat Med 2021; 27(7): 1272–1279
95. Rinott E, Youngster I, Yaskolka Meir A, Tsaban G, Zelicha H, Kaplan A, Knights D, Tuohy K, Fava F, Scholz MU, Ziv O, Reuven E, Tirosh A, Rudich A, Blüher M, Stumvoll M, Ceglarek U, Clement K, Koren O, Wang DD, Hu FB, Stampfer MJ, Shai I. Effects of diet-modulated autologous fecal microbiota transplantation on weight regain. Gastroenterology 2021; 160(1): 158–173.e10
96. de Groot PF, Frissen MN, de Clercq NC, Nieuwdorp M. Fecal microbiota transplantation in metabolic syndrome: History, present and future. Gut Microbes 2017; 8(3): 253–267
97. Ma Y, Xu X, Li M, Cai J, Wei Q, Niu H. Gut microbiota promote the inflammatory response in the pathogenesis of systemic lupus erythematosus. Mol Med 2019; 25(1): 35
98. Ma Y, Niu H. In Gut Microbiota Can Promote the Inflammatory Response in The Pathogenesis of Systemic Lupus Erythematosus. Summary of the 13th National Conference on Immunology, 2018
99. Zhang Y, Liu Q, Yu Y, Wang M, Wen C, He Z. Early and short-term interventions in the gut microbiota affects lupus severity, progression, and treatment in MRL/lpr mice. Front Microbiol 2020; 11: 628
100. Danne C, Rolhion N, Sokol H. Recipient factors in faecal microbiota transplantation: one stool does not fit all. Nat Rev Gastroenterol Hepatol 2021; 18(7): 503–513
101. Abbasi J. Are bacteria transplants the future of eczema therapy? JAMA 2018; 320(11): 1094–1095
102. Nakatsuji T, Hata TR, Tong Y, Cheng JY, Shafiq F, Butcher AM, Salem SS, Brinton SL, Rudman Spergel AK, Johnson K, Jepson B, Calatroni A, David G, Ramirez-Gama M, Taylor P, Leung DYM, Gallo RL. Development of a human skin commensal microbe for bacteriotherapy of atopic dermatitis and use in a phase 1 randomized clinical trial. Nat Med 2021; 27(4): 700–709