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Eya Toumi, Soraya Mezouar, Anne Plauzolles, Laurent Chiche, Nathalie Bardin, et al.. Gut microbiota in SLE: from animal models to clinical evidence and pharmacological perspectives. *Lupus science & medicine*, 2023, 10 (1), pp.e000776. 10.1136/lupus-2022-000776 . hal-04082348

**HAL Id: hal-04082348**

**<https://amu.hal.science/hal-04082348>**

Submitted on 22 Jan 2024


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# Gut microbiota in SLE: from animal models to clinical evidence and pharmacological perspectives

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**To cite:** Toumi E, Mezouar S, Plauzolles A, *et al.* Gut microbiota in SLE: from animal models to clinical evidence and pharmacological perspectives. *Lupus Science & Medicine* 2023;**10**:e000776. doi:10.1136/lupus-2022-000776

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Received 21 September 2022  
Accepted 16 December 2022



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## ABSTRACT

Systemic lupus erythematosus (SLE) is a multifactorial autoimmune disease driven by complex interactions between genetics and environmental factors. SLE is characterised by breaking self-immune tolerance and autoantibody production that triggers inflammation and damage of multiple organs. Given the highly heterogeneous nature of SLE, the treatments currently used are still not satisfactory with considerable side effects, and the development of new therapies is a major health issue for better patient management. In this context, mouse models significantly contribute to our knowledge of the pathogenesis of SLE and are an invaluable tool for testing novel therapeutic targets. Here, we discuss the role of the most used SLE mouse models and their contribution to therapeutic improvement. Considering the complexity of developing targeted therapies for SLE, adjuvant therapies are also increasingly proposed. Indeed, murine and human studies have recently revealed that gut microbiota is a potential target and holds great promises for successful new SLE therapies. However, the mechanisms of gut microbiota dysbiosis in SLE remain unclear to date. In this review, we propose an inventory of existing studies investigating the relationship between gut microbiota dysbiosis and SLE to establish microbiome signature that may serve as a potential biomarker of the disease and its severity as well as a new potential therapy target. This approach may open new possibilities for early diagnosis, prevention and therapeutic perspectives of SLE based on gut microbiome.

## INTRODUCTION

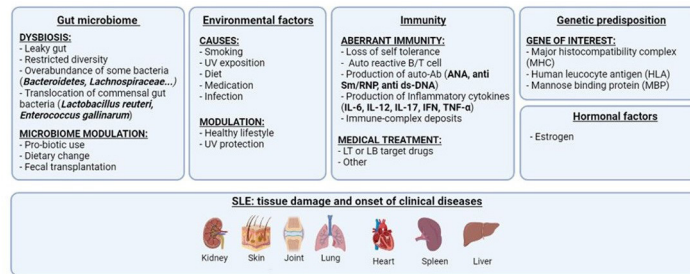
SLE is a chronic and complex autoimmune disease affecting multiple organ systems including skin, joint, kidney and lung.<sup>1</sup> SLE is most often diagnosed in young women of reproductive age and marked by remissions and relapse stages.<sup>2,3</sup> The aetiology of SLE remains unclear but likely involves hormonal, environment and genetic factors (figure 1). The impairment of central and peripheral tolerance is critical for the pathogenesis of SLE leading to the production of autoantibodies typically against nuclear antigens and that of immune complexes (ICs). IC

deposition in target organs initiates and maintains an inflammatory environment, resulting in a wide range of symptoms that may be mild, moderate or severe.<sup>4</sup> Lupus nephritis is the most common complication of the disease and the major risk factor for mortality and morbidity in SLE.<sup>5</sup>

Because of the clinical heterogeneity of the disease and the complexity of its immune mechanisms, treatment of SLE remains challenging. As no curative therapy is yet available, current standards of care for patients with SLE involve corticosteroids, immunosuppressive drugs, non-steroidal anti-inflammatory drugs (NSAIDs), and antimalarial (hydroxychloroquine) drugs to treat only main symptoms.<sup>6</sup> Unfortunately, these current treatments, used alone or in combination, are not specific and present several undesirable side effects including the risk of developing severe infections.<sup>7</sup> Hence, the development of new therapies constitutes today a major health issue that needs to be addressed to provide better management of patients with SLE and to improve their quality of life and survival.

Various mouse models provide significant insights into the comprehension of the SLE pathogenesis and the development of new treatments.<sup>8</sup> Due to the anatomical and immunological differences between mice and humans and the heterogeneity in the expression of SLE, there is no single mouse model that fully reproduces human SLE.<sup>9,10</sup> Despite numerous existing models, each has its own advantages and disadvantages, offering specific features of interest to address different preclinical objectives.

Recently, the potential impact of the gut microbiota on the disease has attracted the attention of researchers.<sup>11</sup> By definition, a dysbiosis is characterised by (1) a loss of beneficial bacteria, (2) an excessive growth of potentially harmful bacteria or (3) a loss of overall bacterial diversity. Such alterations



**Figure 1** Multifactorial etiology of SLE. The interplay between genetic, hormonal and environmental factors influences gut dysbiosis and dysregulates immune responses leading to SLE pathophysiology. Ab, antibody; dsDNA, double-strand DNA; IFN, interferon; IL, interleukin; LB, lymphocytes B; LT, lymphocyte T; RNP, ribonucleoprotein; Sm, Smith; TNF, tumour necrosis factor; UV, ultraviolet.

in gut microbial composition and functions have been associated with the occurrence and the severity of SLE manifestations, thus indicating that this dysbiosis could take part in the pathophysiology of the disease.<sup>12</sup> Experimental data in mouse models have also underlined how specific microbiome changes affect SLE activity.<sup>13 14</sup> However, whether gut dysbiosis is only the consequence of SLE progression or the cause behind its severity and progression remains unknown. Therefore, it is essential to know how gut bacteria disrupt immune tolerance in SLE in order to seek new therapeutic approaches based on gut microbiota modulation.

In this review, we present an inventory of animal models available to investigate the pathophysiology of SLE (excluding the context of hormonal, genetic and environmental factors). We also propose to evaluate the positioning of the gut microbiota as a biomarker and innovative therapeutic target in patients with SLE.

### COMMON MURINE MODELS OF LUPUS

Over the last 50 years, mouse models of lupus have been proven to be an invaluable resource for investigating lupus pathophysiology and studying new therapeutic targets.<sup>9</sup>

#### Spontaneous murine models of lupus

The spontaneous models of lupus in mice are represented by four main strains genetically and immunologically distinct (table 1).

First, the New Zealand black (NZB) and New Zealand white (NZW) crossed strain is referred to as the NZB/NZWF1 or BW model.<sup>15 16</sup> BW mice produce ANA, mainly antidouble-strand DNA (dsDNA), and develop glomerulonephritis associated with ICs and mild vasculitis. Although the BW model presents the advantage to develop mainly in women as observed in human populations, mice develop clinical manifestations late in their life,<sup>16</sup> making the study of SLE via this model long-lasting and costly. This time lapse has been recently reduced through the administration of adenoviruses that express interferon- $\alpha$  or injecting toll-like receptor (TLR)-7 agonists, thus making BW mice more suitable for SLE research.<sup>17 18</sup>

The second strain, the Murphy-Roths-Large (MRL)/lymphoproliferation (lpr) model, was generated by intercrossing several mouse strains including LG, B6, AKR and C3H.<sup>19 20</sup> A spontaneous lpr mutation is developed and is later seen as a retrotransposon that alters the Fas gene, a major regulator of apoptosis immune cells.<sup>21 22</sup> The MRL/lpr model is unique in developing a full panel of human SLE autoantibodies including ANA, anti-dsDNA, anti-Smith (Sm), anti-Sjogren's syndrome-related antigen A (SSA, also called anti-Ro) and anti-Sjogren's syndrome-related antigen B (SSB, also called anti-La), and has multiple clinical manifestations such as arthritis, cognitive dysfunction, rash and vasculitis. The pr gene significantly accelerates the development and the severity of the disease. This model has been used to study the role of TLR-7 and TLR-9 in lupus<sup>23</sup> and widely used for the evaluation of new therapeutic molecules.<sup>24-26</sup> However, its molecular mechanism is likely different from that observed in human SLE, the former being driven by IFN- $\gamma$  and the second by IFN- $\alpha$ .<sup>27</sup>

The third model, MRL<sup>+</sup> mice, lacks the Fas mutation and consequently develops milder lupus at a later stage.<sup>19</sup> This model is used primarily to study accelerants of disease.

Finally, the fourth model is that of BXSB mice that differs from other models because the disease develops in males due to a genetic risk located on the Y chromosome<sup>28</sup> and manifests only by a glomerulonephritis. Despite these constraints, the BXSB model allows the evaluation of TLR-7 driven mechanisms, which are key mechanisms involved in the SLE pathophysiology.<sup>29</sup>

#### Induced models of murine lupus

Unlike mouse models of spontaneous lupus mentioned previously in which genetic factors play a major role, lupus could be developed by exposure of healthy mice to certain environmental agents. These induced models give further insights into the role of environmental factors that may predispose to SLE.<sup>30 31</sup> They also allow the study of initial events leading to a break in tolerance in the absence of genetic defects, providing a better understanding of the cellular mechanisms involved in SLE development and progression.<sup>31</sup> When administered

**Table 1** Clinical mouse models of lupus

Mouse model	Clinical manifestation						References	
	Autoantibodies	Glomerulonephritis	Arthritis	Skin rash	Others	Advantages		Disadvantages
Spontaneous models	NZB/NZW F1 (BW) ▲ ANA. ▲ Anti-dsDNA.	Active proliferative (4–5 months)	Absent	Absent	Vasculitis	Accelerated by IFN	▲ Slow disease progression. – Requires cross of two strains to generate the model	<sup>15–16</sup>
MRL/lpr	▲ ANA (anti-Sm, anti-Ro and anti-La). ▲ Anti-dsDNA.	Active proliferative (3–4 months)	Microscopic synovitis	Rash on face and back	Cognitive dysfunction, vasculitis and oophoritis	Early and severe disease onset with several clinical manifestations observed in humans	▲ Fas mutation does not drive human SLE. ▲ SLE is not driven by IFN- $\alpha$ .	<sup>20</sup>
MRL/+	▲ ANA. ▲ Anti-dsDNA.	Nephritis (very late in life)	Mild microscopic synovitis	Mild dermatitis	Late cognitive dysfunction		Develop milder lupus at a later stage	<sup>19</sup>
BXSB	▲ ANA (anti-nucleolar). ▲ Anti-dsDNA.	Proliferative (4–5 months)	Absent but neutrophilic infiltrate in joints	Absent		Evaluation of TLR-7 driven mechanisms	Male predominance contrary to the human SLE	<sup>28</sup>
Induced models	Pristane ▲ ANA (anti-SnRNP and anti-Su). ▲ Anti-dsDNA.	Active proliferative nephritis (6–8 months post induction)	Erosive arthritis	Rash on face	Hepatitis, pulmonary vasculitis, anaemia and serositis	Induced in non-autoimmune strain Predictable timing	▲ Difference susceptibility between strains. ▲ Slow clinical manifestation onset.	<sup>32–34</sup>
Resiquimod	▲ ANA. ▲ Anti-dsDNA.	Proliferative nephritis (at 4 weeks post induction)	Absent	Absent	Splenomegaly, carditis, hepatitis	No gender predominance Rapid onset	Limited organ manifestation	<sup>36</sup>
Imiquimod	▲ ANA. ▲ Anti-dsDNA.	Proliferative nephritis	Absent	Dermatitis	Atherosclerosis			

BW, black-white; dsDNA, anti-double stranded DNA; Fas, cell surface death receptor; IFN, interferon; lpr, lymphoproliferation; MRL, Murphry-Roths-Large; NZ, New Zealand; Sm, Smith; SnRNP, small nuclear ribonucleoprotein; TLR, toll-like receptor.

to BALB/c mice by the intraperitoneal route, the mineral oil pristane (2,6,10,14 tetramethylpentadecane) induces a panel of human SLE symptoms from a few days to several months.<sup>32</sup> These symptoms include ICs glomerulonephritis, erosive arthritis, skin rash and, in more severe cases, pulmonary vasculitis and haemorrhage. Numerous SLE-associated autoantibodies such as ANA, anti-dsDNA, anti-SnRNP are also observed.<sup>33,34</sup> Interestingly, pristane-induced lupus (PIL) is characterised by the overproduction of type I IFN, a mechanism often observed in patients with SLE.<sup>35</sup> Resiquimod or imiquimod creams containing TLR-7 ligand have been more recently used to induce murine lupus after administration to the ears of specific strains of mice. The SLE-like disease develops within 2–4 weeks without sex predominance but is limited to few organs and does not reflect the systemic nature of the disease.<sup>36</sup>

## SLE AND GUT MICROBIOME DYSBIOSIS

### Murine models of lupus and gut microbiota

Despite the imperfection of murine models of lupus, they are useful to understand the pathophysiology of SLE. Besides the high genetic similarity, the mouse have some similarity to humans in gut microbial taxonomy, making it an interesting murine model for assessing host–microbiota interactions applicable to humans.<sup>37,38</sup> First, the potential role of gut microbiota in SLE has been reported for the first time with the PIL mice model. In 1998, Hamilton *et al* indicated that the production of autoantibodies is lower and delayed in specific pathogen-free mice compared with conventionally housed mice, demonstrating that murine lupus is favoured in a microbial environment.<sup>39</sup> Then different mouse models confirmed the role of gut microbiota in the development of lupus and showed that gut permeability and bacterial translocations favour disease progression (table 2). Second, it has been found that female mice are 10 times more affected than male mice in murine lupus,<sup>40,41</sup> confirming the gender-related prevalence of SLE in humans.<sup>42</sup> Third, the severity of symptoms in MRL/lpr female mice is inversely and positively related to the relative abundance of Lactobacillaceae and Lachnospiraceae, respectively.<sup>40</sup>

The mechanisms governing the relationship between murine models of lupus and gut microbiota begin to be understood. *Lactobacillus* genus is the most studied in lupus models. Some species of the *Lactobacillus* used as probiotics regulate immune and anti-inflammatory responses through reduction of IL-6 and enhancing IL-10.<sup>13,43</sup> Treatments with dietary retinoic acid (RA, vitamin A) of female mice improve clinical symptoms of the disease by restoring intestinal colonisation by *Lactobacillus* species,<sup>40</sup> suggesting that *Lactobacillus* plays a preventive role in the development of murine lupus. The *Lactobacillus* supplementation also reduces proteinuria and autoantibody levels and improves renal pathology scores in MRL/lpr mice with lower inflammatory cytokines, higher anti-inflammatory cytokines and increased

number of Tregs.<sup>13</sup> *Lactobacillus casei* or *L. reuteri* feeding retards nephritis and improves survival in BW model of lupus,<sup>44</sup> whereas *L. fermentum* feeding reduces cardiovascular complications.<sup>45</sup> Other studies have reported contradictory results. The relative abundance of *Lactobacillus* increases considerably during disease development and is related to an impaired renal function and a higher systemic autoimmunity.<sup>46</sup> Zegarra-Ruiz *et al* showed that *L. reuteri* exacerbates the disease in murine models dependent on TLR-7 or induced by imiquimod, and *L. reuteri* and *L. johnsonni* bacteria are translocated to internal organs. Only *L. reuteri* induces IFN gene signature with systemic autoimmunity.<sup>47</sup> This inconsistency in findings may be due to several factors. The *Lactobacillus* genus includes numerous species that may play many different roles in the pathogenesis of murine lupus. The translocation of bacteria may also play an important role. Indeed, the translocation of *Enterococcus gallinarum* from gut to liver and other organs leads to an autoimmune response such as IFN expression and anti-dsDNA production in lupus.

As shown in table 2, the bacterial populations recovered differ between murine studies. This may be explained by the genetic differences between different mouse models which seems to have a significant impact on the microbial composition. In fact, the genetic and environmental factors were found associated with several variations in the gut microbiota of laboratory mice.<sup>48,49</sup> Thus, comparative analyses should be moderate between genetically modified mice and/or with human cohorts.

### Human SLE cohorts and gut microbiota

Emerging investigations confirmed the role of gut microbiota dysbiosis in patients with SLE as shown in table 3.

First of all, as shown in table 3, most studies were performed in American or Asian populations. It was shown that the amount of faecal microbial community varied according to geographical area. At the phylum level, Firmicutes were more abundant in the American population than in the other countries, while *Actinobacteria* increased more in the Japanese population. Korean and Japanese subjects had also a gut microbiota rich in Bacteroidetes.<sup>50</sup> This strong geographical influence is mainly due to dietary diversity and the associated eating habits which have a strong impact on microbial composition.<sup>51</sup> Indeed, it has been shown that the *Bacteroides* enterotype is more common in the gut of people living in Western countries with a high-fat, high-protein western diet, whereas the *Prevotella* enterotype is common in non-Western countries with a high-fibre intake.<sup>52</sup> This suggests that the country of origin should be reported in comparisons of the microbiota in humans with additional caution in comparative analyses between cohorts of different countries.

Most of the studies have been performed in women and show reduced and increased abundances of Firmicutes and Bacteroidetes, respectively, even in remission phase of SLE<sup>53–57</sup> as well as a decrease in overall biodiversity.<sup>56</sup>

**Table 2** Gut microbiota in mouse models of lupus

Mice	Main results compared with control mice	Correlation with severity of lupus symptoms		References
		+	-	
MRL/lpr	↑ Lachnospiraceae, Ruminococcaceae and Rikenellaceae	Lachnospiraceae Rikenellaceae	Lactobacillaceae	40
	↓ Lactobacillaceae and <i>Bifidobacterium</i> ↑ <i>Blautia</i> , <i>Ruminococcus torques</i> ↓ <i>Desulfovibrio</i>			65
SNF1	↑ Bacteroidetes ↑ <i>Turicibacter</i> and <i>Lactobacillus reuteri</i> in mice given acidic pH water Acidic pH water has accelerated nephric damage.	Bacteroidetes Rikenellaceae		79
	↓ <i>Verrucomicrobia</i> , <i>Dysgonomonas</i> ↑ <i>Bacteroides</i> , <i>Parabacteroides</i> Gender-specific difference in gut microbiota at adult age			41
MRL/lpr	↓ Lactobacillales		<i>Lactobacillus</i> (correct the leaky gut and improve renal function)	13
	↑ Bacteroidetes ↓ Firmicutes, Clostridia, <i>Clostridiales</i> and Lachnospiraceae Reduction in microbial diversity Butyrate treatment ameliorates kidney damage			104
NZB/W F1	↑ <i>Clostridium</i> , <i>Lactobacillus</i> , <i>Dehalobacterium</i> , <i>Oscillospira</i> , <i>Dorea</i> , <i>Bilophila</i> and <i>AF12</i> (Ruminococcaceae) ↓ <i>Akkermansia muciniphila</i> and <i>Anaerostipes</i>	<i>Lactobacillus</i>		46
NZW×BXSBF1	↑ <i>Enterococcus gallinarum</i>	<i>E. gallinarum</i>		68
TLR7-dependent spontaneous and induced mice	↑ <i>L. reuteri</i>	<i>L. reuteri</i> (increase plasmacytoid dendritic cell and interferon response)		47
TC lupus prone	↑ <i>Turicibacter</i> ↓ <i>Alistipes</i> (Rickenellaceae) and <i>Lactobacillus</i> FMT from lupus mice to GF mice induces anti-dsDNA antibodies and immune response.			14
	↑ Prevotellaceae, <i>Paraprevotelle</i> , <i>Lactobacillus</i>			105

↑, increased; ↓, decreased; +, positively correlated with disease, -, negatively correlated with disease.  
dsDNA, anti-double stranded DNA; FMT, fecal microbiota transplantation; GF, germ-free; lpr, lymphoproliferation; MRL, Murphy Roths Large; NZB/W, New Zealand black/white; SNF1, sucrose non-fermenting 1; TC, transchromosomal; TLR, toll-like receptor.

In addition, reduced levels of IFN in patients with SLE have been associated with a lower Firmicutes to Bacteroidetes ratio (F:B) and fewer Firmicutes, which are responsible of inflammatory reactions in patients with SLE. This F/B imbalance seems to be the main feature of SLE dysbiosis regardless of lifestyle, disease duration/ stage or diet. Other bacterial phyla are altered in patients with SLE with increased *Proteobacteria*<sup>46 56 58</sup> and *Actinobacteria*,<sup>40</sup> and decreased *Synergistetes*<sup>59</sup> and *Tenericutes*.<sup>60</sup>

Significant differences in bacterial genera have also been observed. The abundance of *Rhodococcus*, *Eubacterium*, *Flavonifractor*, *Eggerthella*, *Klebsiella* and *Prevotella* is significantly higher in patients with SLE compared with the control group, whereas *Pseudobutyriivibrio* and *Dialister* are decreased.<sup>54</sup> Other studies reported a decrease of some beneficial bacteria such as *Odoribacter*,<sup>46</sup> *Roseburia*, *Bifidobacterium* and *Faecalibacterium prausnitzii*,<sup>60</sup> these bacteria playing multiple roles in maintaining the homeostasis

**Table 3** Gut microbiota in patients with SLE

Country	Cohort (W:M)	Main results in patients with SLE compared with HCs	References
Spain	20 SLE (20:0) vs 20 HCs (20:0)	↓ F:B ratio	53
China	45 SLE (45:0) vs 48 HCs (45:0)	↓ F:B ↑ <i>Rhodococcus</i> , <i>Eggerthella</i> , <i>Klebsiella</i> , <i>Prevotella</i> , <i>Eubacterium</i> and <i>Flavonifractor</i> ↓ <i>Dialister</i> and <i>Pseudobutyrvibrio</i>	54
China	92 SLE (NI) vs 217 HCs (NI)	↑ Bacteroidetes, <i>Proteobacteria</i> , <i>Actinobacteria</i> ↓ Firmicutes ↑ <i>Ruminococcus</i> , <i>Klebsiella</i> , Erysipelotrichaceae (correlation of <i>Ruminococcus</i> with the Treg counts in peripheral blood) ↓ <i>Faecalibacterium</i>	71
USA	16 SLE (16:0) vs 11 sex-matched HCs	↓ F:B <i>Bacteroides thetaiotaomicron</i> expressed anti-Ro60 antibodies	55
USA	14 SLE (10:4) vs 17 sex-matched HCs	No difference in F:B ↑ <i>Proteobacteria</i> and <i>Blautia</i> ↓ <i>Odoribacter</i>	46
Netherland	30 SLE (28:2) vs 965 sex-matched HCs	↓ Bacterial richness ↓ F:B ↑ Bacteroidetes, <i>Proteobacteria</i> , <i>Bacteroides</i> , <i>Alistipes</i> , <i>B. vulgatus</i> , <i>B. uniformis</i> , <i>B. ovatus</i> and <i>B. thetaiotaomicron</i>	56
USA	12 SLE (12:0) vs 22 HCs (12:0)	↑ <i>Lactobacillus spp</i>	47
USA	61 SLE (61:0) vs 17 HCs (17:0)	↓ Bacterial richness mostly in patients with higher SLEDAI ↑ <i>Ruminococcus gnavus</i> , Lachnospiraceae, Veillonellaceae Anti-RG antibodies related to disease activity and lupus nephritis ↑ Faecal calprotectin levels	64
China	14 SLE (13:1) vs 16 HCs (14:2)	↑ <i>Proteobacteria</i> , Enterobacteriaceae, <i>Streptococcus</i> ↓ Ruminococcaceae, Prevotellaceae, <i>Prevotella</i> , <i>Roseburia</i> , <i>Ezakiella</i>	58
China	40 SLE (40:0) (19 active and 21 remissive) vs 20 HCs (20:0)	↓ F:B ↑ Streptococaceae, Lactobacillaceae, <i>Streptococcus</i> , <i>Lactobacillus</i> and <i>Megasphaera</i> ↓ <i>Faecalibacterium</i> and <i>Roseburia</i> Positive association of <i>Streptococcus</i> , <i>Campylobacter</i> and <i>Veillonella</i> with lupus activity Negative association of <i>Bifidobacterium</i> with lupus disease activity	60
China	21 SLE (21:0) vs 10 HCs (10:0)	↑ F:B with ↓ Bacteroidetes ↑ <i>Proteobacteria</i> , Enterococcaceae, <i>Escherichia Shigella</i> ↓ Ruminococcaceae, Clostridia and <i>Faecalibacterium</i>	106
China	17 SLE (17:0) vs 20 HCs (20:0)	Positive correlation of <i>Bacteroides</i> , <i>Bilophila</i> , <i>Parabacteroides</i> and <i>Succinivibrio</i> with the levels of proinflammatory IL-17, IL-21, IL-2R, IL-35, IFN and IL-10 ↓ <i>Dialister</i> , <i>Gemmiger</i> negatively correlated with IL-17, IL-2R and IL-35 ↓ F:B	57
China	117 SLE vs 115 HCs	↑ <i>Clostridium</i> sp ATCC BAA-442, <i>Atopobium rima</i> , <i>Shuttleworthia satelles</i> , <i>Actinomyces massiliensis</i> , <i>Bacteroides fragilis</i> , <i>Clostridium leptum</i> <i>Odoribacter splanchnicus</i> and <i>Akkermansia muciniphila</i> were highly similar to Sm antigen, Fas antigen epitopes and autoantibodies production	65
China	33 SLE vs 28 HCs	↑ <i>Proteobacteria</i> , Enterobacteriales ↓ Ruminococcaceae	106

Continued

**Table 3** Continued

Country	Cohort (W:M)	Main results in patients with SLE compared with HCs	References
France	16 SLE vs 76 HCs	↓ <i>Tenericutes</i> ↑ <i>Alistipes</i> , <i>Flintibacter</i> , <i>Tannerellaceae</i> , <i>Parabacteroides</i> and <i>Alistipes onderdonkii</i>	107

↑, increased; ↓, decreased.

F:B, Firmicutes to Bacteroidetes ratio; HC, healthy control; IFN, interferon; IL, interleukin; M, men; NI, no information (the sex of patients with SLE is not mentioned); RG, *Ruminococcus gnavus*; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; Sm, Smith; Treg, T regulatory cell; W, women.

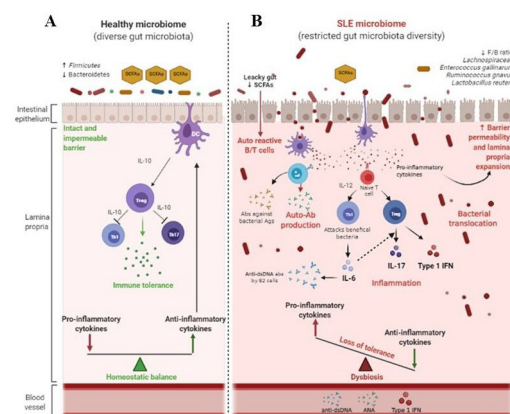
in the human body through the provision of energy and nutrients,<sup>61</sup> reducing inflammation<sup>62</sup> and protecting the intestinal barrier.<sup>63</sup> Interestingly, the relative abundance of *Lactobacillus* spp, particularly *L. mucosae*, is increased in patients with SLE,<sup>47</sup> confirming previous human and animal data that show that *Lactobacillus* plays a role in the pathogenesis of SLE.<sup>13,60</sup> It has also been shown that *Streptococcus anginosus* and *Veillonella* are significantly elevated in patients with SLE and related to the disease activity.<sup>60</sup> The overabundance in women with SLE of *Ruminococcus gnavus*, which belongs to the Lachnospiraceae family, also reflects the extent of the disease activity in patients with lupus nephritis.<sup>64</sup> The study of the relationship between the gut microbiota composition and the cytokine profile in patients with SLE shows that the increase of certain bacterial genera such as *Bacteroides*, *Bilophila*, *Parabacteroides* and *Succinivibrio* is related to the levels of inflammatory cytokines including IL-17, IL-21, IL-2R, IL-35, IFN and IL-10, suggesting that these bacteria play a role in stimulating inflammatory response. However, *Dialister* and *Gemmiger* genera are reduced in patients with SLE and show a negative association with IL-17, IL-2R and IL-35 levels, suggesting a potential protective role of these bacterial genera via the reduction of inflammatory cytokines.<sup>57</sup>

In parallel, it has been shown that the production of autoantibodies can result from the molecular mimicry with different bacterial populations in SLE. Indeed, bacteria was found mimicking orthologue epitopes similar to host protein, activating autoimmune T and B cells. Indeed, Greiling *et al* found that gut commensal *Bacteroides thetaioamicron* expressed human anti-Ro60 antibodies and delivered antigens to immune cells.<sup>55</sup> In addition, sera from anti-Ro60-positive patients with SLE immunoprecipitated bacterial ribonucleoprotein complexes containing Ro60 orthologues.<sup>55</sup> More recently, it has been shown that peptides produced by *Odoribacter splanchnicus* and *Akkermansia muciniphila* bacteria are highly similar to Sm antigen and Fas antigen epitopes. Interestingly, peptides from these bacteria can activate CD4<sup>+</sup> T cells or B cells to produce autoantibodies.<sup>65</sup>

### Gut microbiota and pathogenesis of SLE

Under physiological conditions, the gut barrier integrity is maintained with a diversified and balanced microbial profile. The bacterial production of short chain fatty acids (SCFAs) ensures normal differentiation of T

lymphocytes and B lymphocytes and maintain immune self-tolerance by modulating Treg cells.<sup>66</sup> Firmicutes bacteria are the main producers of butyrate, which plays a central role in the generation and maintenance of Treg cells in various tissues, especially in the gut.<sup>67</sup> They block the transdifferentiation of T cells into Th17 effectors and Th1 cells and ensure a balanced production of both anti-inflammatory and inflammatory cytokines (figure 2A). It has been shown that the impaired intestinal barrier



**Figure 2** Proposed representation of the interplay between gut microbiota and systemic immunity in the pathogenesis of SLE. (A) Under symbiosis conditions (healthy microbiome), the gut barrier is intact with a diversified and balanced microbial profile. SCFA bacterial production ensures normal differentiation of immune cells (T and B cells) and maintains immune self-tolerance by regulating Treg cells by balanced Th1/Th17 as well as the production of anti-inflammatory cytokines. (B) The gut dysbiosis is frequently characterised by changes in the Firmicutes associated with a restricted diversity of gut microbiota and an increased gut permeability ('leaky gut') leading to immune dysregulation. Bacterial translocations increase their antigen exposure in lamina propria with autoreactive T and B cells leading to overactivation of Treg cells and Th17 transdifferentiation. This process promotes the production of a wide variety of proinflammatory cytokines (IL-6 and IL-17) and auto-ABs (ANA and anti-dsDNA) as well as type 1 IFN. All these circulating inflammatory products lead to loss of autotolerance, excessive immunological reaction and tissue/organ destruction. Ab, antibody; Ag, antigen; DC, dendritic cell; dsDNA, double-strand DNA; F:B, Firmicutes to Bacteroidetes ratio; IFN, interferon; IL, interleukin; SCFA, short-chain fatty acid; Th, T helper; Treg, regulatory T cell.



function observed in SLE leads to gut permeability, which is called 'leaky gut'.<sup>64</sup> An increased abundance of bacteria such as *R. gnavus*<sup>64</sup> and *E. gallinarum*<sup>68</sup> leads to the release of inflammatory factors that aggravate systemic inflammation. The bacterial translocation into the lumina propria with autoreactive T and B cells stimulate the toll-like pathway and the production of inflammatory cytokines, type I IFN and autoantibodies. Those circulating inflammatory products lead to the loss of tolerance and organ damages<sup>69–71</sup> (figure 2B).

## CHALLENGES IN THE TREATMENT OF SLE

### Failure of standard treatments of SLE

The treatments of SLE represents a challenge due to the heterogeneity of disease manifestations and clinical courses.<sup>72</sup> Few therapeutic options exist for disease control including corticosteroids, anti-malarial drugs, NSAIDs and often immunosuppressives drugs for severe diseases.<sup>73</sup> These treatments fail to provide a cure and are associated with numerous side effects and substantial toxicity. The long-term outcome of patients with severe SLE is still unsatisfactory.<sup>6</sup> A major health issue is to develop a curative therapy targeting different components of the immune system through mouse models before clinical trials.<sup>8,9</sup> New treatments are being developed, in particular, new biotherapies to reduce adverse effects of standard treatments and improve the prognosis in the long term. The new therapeutic agents target mainly B cells, T cells and cytokine pathways, that are key players in lupus disease.<sup>9</sup> Their approaches vary from targeting cell surface markers of B cells (CD20 or CD22) to targeting cytokines and signalling molecules (such as B-cell activating factor (BAFF), IL-6, IL-17 or IL-2), costimulatory molecules including inducible T-cell costimulator (ICOS) or interactions between co-stimulatory molecules (such as CD40-CD40L).<sup>74</sup> Among the available interventions, monoclonal antibodies (mAbs) are the most studied: they allow either to deplete B cells using anti-CD20 mAbs (rituximab, ofatumumab, ocrelizumab and veltuzumab) or to modulate their functions using mAbs directed against BAFF (belimumab and tabalumab).<sup>6</sup> These therapeutic agents were initially promising in preclinical murine studies or early clinical phases but failed in late-phase trials. Only belimumab has been approved to treat patients with SLE with persistent activity.<sup>75,76</sup> The failures in preclinical phases may be related to the choice of mouse models. Indeed, the evaluation of therapeutic approaches is largely dependent on the model of murine lupus since the effects of the same treatment are different according to the mouse model used.<sup>77</sup> This implies that preclinical studies must be validated in several murine models. Also, the implementation of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) in murine studies should be considered as this score is used in the therapy management of patients with SLE. Hence, it appears important to introduce this parameter in future murine studies in order to

evaluate new therapeutic molecules according to a clinical or/severity score defined beforehand. Regarding the failure of clinical trials, several factors should include the study design, the sample size, the disease complexity and heterogeneity, geographical and ethnic differences, or duration of the follow-up.<sup>6</sup>

### Therapeutic use of gut microbiome on SLE

Given the unsatisfactory treatment regimen for SLE and the failure of new biotherapies, clinicians are looking for adjuvant therapies that may be used without adverse effects. As the gut microbiota is considered to play an important role in SLE pathophysiology, it may be useful to control disease activity through adapted diet, probiotics or faecal transplantation.<sup>78</sup>

### Dietary intervention in SLE

Diet modification has been shown to play a role in the manifestation of SLE symptoms as one of the main environmental factors with known effects on gut microbiota. The beneficial effect of the acidic pH of drinking water in disease progression is observed in lupus mice.<sup>79</sup> Research focusing on the influence of supplementation in vitamin, polyunsaturated fatty acids (PUFAs) and phytoestrogens also shows a decrease in proteinuria and glomerulonephritis in murine models of lupus.<sup>80</sup> In patients with SLE, caloric restriction and moderate protein intake are beneficial to the immune system efficiency, prevent SLE progression<sup>81</sup> and reduce the level of fatigue.<sup>82</sup> Furthermore, fibre intake regulates hyperlipidaemia, lower blood pressure and C reactive protein (CRP).<sup>83</sup> A higher level of PUFAs attenuates symptoms in women with SLE, reduces antiphospholipid syndrome and improves their clinical status.<sup>81</sup> Omega-3 PUFAs have been studied for the treatment of SLE because they reduce cardiovascular risk.<sup>84</sup> They also have a beneficial effect against SLE by reducing the levels of CRP, anti-dsDNA, IL-1, IL-12<sup>85</sup> and TNF<sup>86</sup> and by regulating proteinuria,<sup>87</sup> haematuria and blood pressure.<sup>88</sup> Vitamins have also an important role in the immune system homeostasis.<sup>89</sup> In patients with SLE, the deficit of vitamins D, an important antioxidant, is associated with more severe disease activity.<sup>90</sup> Vitamin C supplementation prevents cardiovascular complications and reduces inflammation and antibody level.<sup>83</sup> RA, a vitamin A metabolite, also reduces antibody levels, proteinuria and renal function in patients with lupus nephritis.<sup>91</sup>

It is likely that an adequate diet increases the period of remission of SLE, prevents adverse effects of medication, especially systemic corticosteroid therapy, and improves the patient's physical and mental well-being.<sup>88</sup> Further prospective studies are needed on larger cohorts of patients to quantify the long-term impact of diet on SLE and to determine whether a diet modulation, likely less expensive and safer than immunosuppressive drugs, might become a cost-effective approach for the management of SLE.

### Probiotic interventions in SLE

Another microbial therapeutic approach is the use of probiotics, live commensal microorganisms, known to affect immune homeostasis by keeping a healthy microbial balance.<sup>92</sup> There is growing evidence supporting that the long-term use of some probiotics regulates the inflammatory state and reduces the production of autoantibodies and SLE progression.<sup>93</sup> As different strains of *Lactobacillus*<sup>94</sup> and *Bifidobacterium* impact some autoimmune diseases,<sup>95</sup> experimental and clinical trials have been conducted on SLE. SLE microbiota are in some cases poor in the probiotic genera *Bifidobacterium* and *Lactobacillus*. These two types of bacteria are among the most abundant beneficial bacteria in the human gut microbiota that produce SCFAs via dietary fibre fermentation.<sup>96</sup> Also, it has been reported that *Bifidobacterium* prevents excessive activation of CD4<sup>+</sup> T cells and thus maintains the balance of Treg, Th17 and Th1 cells in patients with SLE.<sup>59</sup> Furthermore, the supplementation by *Bifidobacterium bifidum*, one of the most common probiotic bacteria, prevents CD4<sup>+</sup> T-lymphocyte overactivation in patients with SLE. The therapeutic effect of the *L. casei shirota* strain, isolated from healthy human faeces, has been evaluated on MRL/lpr mice. This supplementation leads to an immunomodulation that accelerates macrophage infiltration without affecting the T-cell functions and ultimately prolonged MRL/lpr mice lifespan.<sup>97</sup> The supplementation by *Lactobacillus* spp in MRL/lpr mice displays a striking effect that prevents lupus nephritis and prolongs survival of mice by reducing anti-dsDNA levels.<sup>13</sup> *L. delbrueckii* subsp *lactis* PTCC 1743 improves the disease symptoms in a PIL mouse model and decreases Th17 cell populations and IL-17a, the latter being involved in the development and maintenance of inflammation.<sup>98</sup> Also, *L. rhamnosus*, ATCC 9595, modulates RA receptor-related orphan receptor gamma, a transcription factor involved in the maturation of Th17 lymphocytes, which would support the decrease observed in this cell population. We hypothesise that the supplementation by these SCFAs-producing bacteria in patients with SLE could be a new therapeutic approach for the treatment of SLE.

### Fecal microbiota transplantation (FMT) and SLE

FMT, which consists in the transfer of gut microbiota from a healthy donor to a patient, has been successfully used in *Clostridium difficile* infection.<sup>99</sup> Increasing number of studies show that FMT presents promising clinical indications for the treatment of many disorders related to gut microbial dysbiosis.<sup>100</sup> Only few studies concern murine lupus and SLE. The FMT from mice with lupus into germ-free mice induce the production of anti-dsDNA antibodies, stimulates inflammatory response, and upregulates the expression of SLE susceptibility gene related to type I IFN and the innate immune response.<sup>14</sup> FMT attenuates lupus severity in mice initially treated with antibiotics by restoring the antibiotic-induced gut microbiota dysbiosis. However, faecal transplantation before lupus onset inhibits the therapeutic efficiency of

glucocorticoids.<sup>71</sup> Untreated mice with lupus that receive FMT from prednisone-treated mice present attenuated lupus-like disease without any side effect of the treatment<sup>101</sup> comforting the idea that FMT could constitute a suitable therapy for SLE. Taken together, these results suggest that gut microbiota could play a direct role in treating SLE or could help in monitoring the therapeutic efficiency of drugs on SLE. Additional experiments are necessary to determine which specific microbial species are involved in the pathogenesis of SLE. For humans, an FMT has been performed on one 34-year-old Mexican woman suffering from SLE with glomerulonephritis, weight loss and malnutrition. An improvement has been observed with reduced diarrhoea and anxiety.<sup>102</sup>

More recently, a first clinical trial of oral FMT capsules was performed in 20 patients with active SLE during 12 weeks. No serious adverse events or deaths were observed. FMT treatment was accompanied by a significant reduction in SLEDAI score and serum anti-dsDNA antibody level. Furthermore, enrichment of SCFAs producing bacterial taxa and reduction of inflammation-related bacterial taxa were identified, along with increased production of SCFAs in the gut and reduced levels of IL-6 and CD4<sup>+</sup> memory:naïve ratio in the peripheral blood. Thus, the FMT switched effectively the gut microbiota community from a proinflammatory state to an-inflammatory state. This study provides evidence that FMT appears to be a safe, feasible and potentially effective treatment modality for SLE.<sup>103</sup> Further clinical studies need to be conducted with a longer follow-up to confirm the long-term safety, effectiveness and potential benefits of FMT-based intervention in SLE. All together will contribute to incorporate new recommendation for patients with SLE in clinical guidelines.

### CONCLUSION

In this review, we discuss the contribution of the main lupus mouse models to understand the complex pathophysiology of SLE. However, therapeutic studies performed on murine models of lupus present some limitations. Similarly, the clinical manifestations of the human disease are heterogeneous and underlining mechanisms are also diverse. This heterogeneity likely explains the failure of various clinical trials to adequately treat patients with SLE and to cure the disease without adverse effects. The gut microbiota dysbiosis is emerging as a source of prognostic, diagnostic biomarkers and potential therapeutic targets for diverse autoimmune diseases. This approach shows some promising results in the treatment of murine lupus and in understanding the underlying cellular and molecular mechanisms. Some recent results suggest that a similar approach in human SLE could improve its treatment but remains to be confirmed on a large scale. We discussed the role of the gut microbiota in SLE pathogenesis, and we reported the different bacterial populations associated with the disease through human and murine studies. Today, prospective, longitudinal and comparative

studies are necessary to establish a robust microbiome signature of SLE that may serve as a biomarker predicting active disease and open new possibilities for diagnostic, preventive and therapeutic approaches. We believe that defining such signature will lead towards a personalised medicine in which gut microbiota profile could constitute a promising tool for clinical practice based on microbiota modulation.

**Contributors** Writing and original manuscript preparation: ET. Review and editing: SM, AP and JLM. Final manuscript validation: ET, SM, AP, LC and JLM. Supervision: JLM and PH. Funding acquisition: PH. All authors contributed to the article and approved the submitted version.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent for publication** Not applicable.

**Ethics approval** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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