Lupus Nephritis and Microbiome

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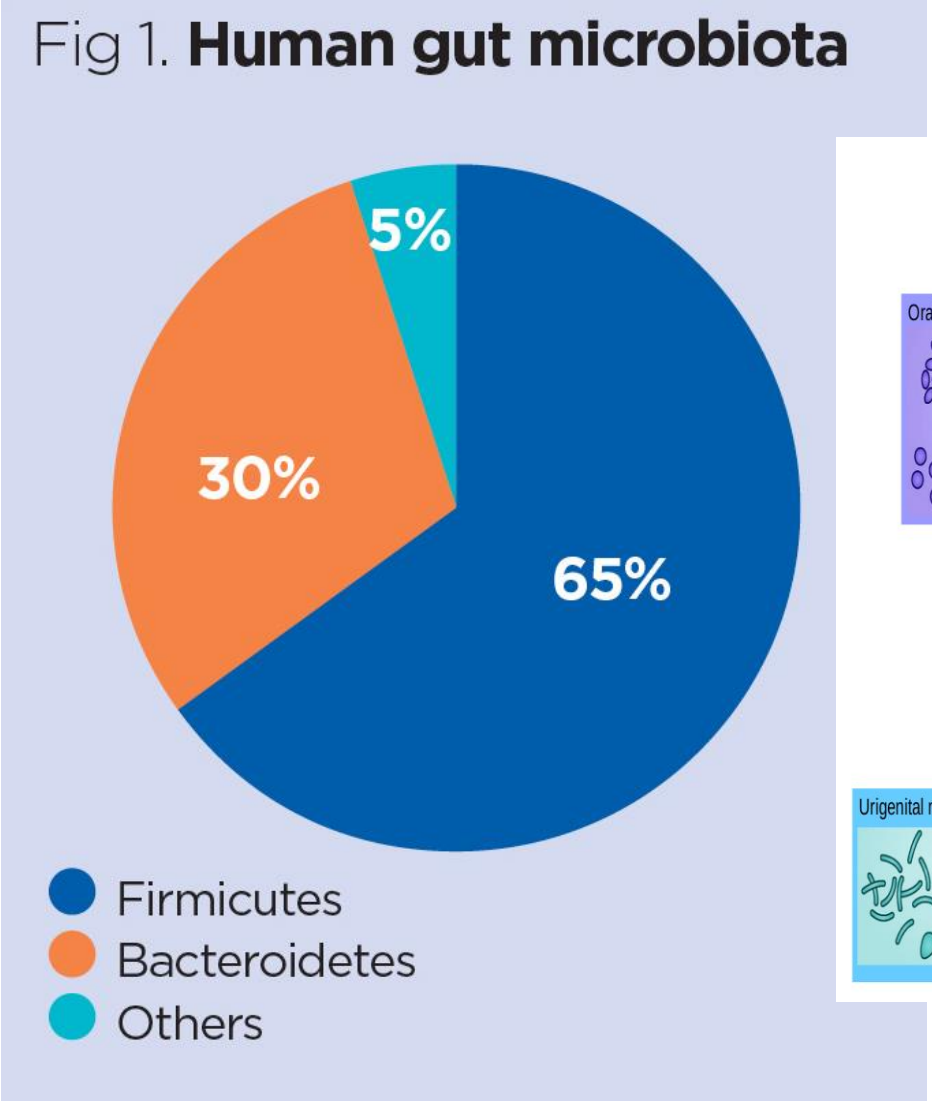
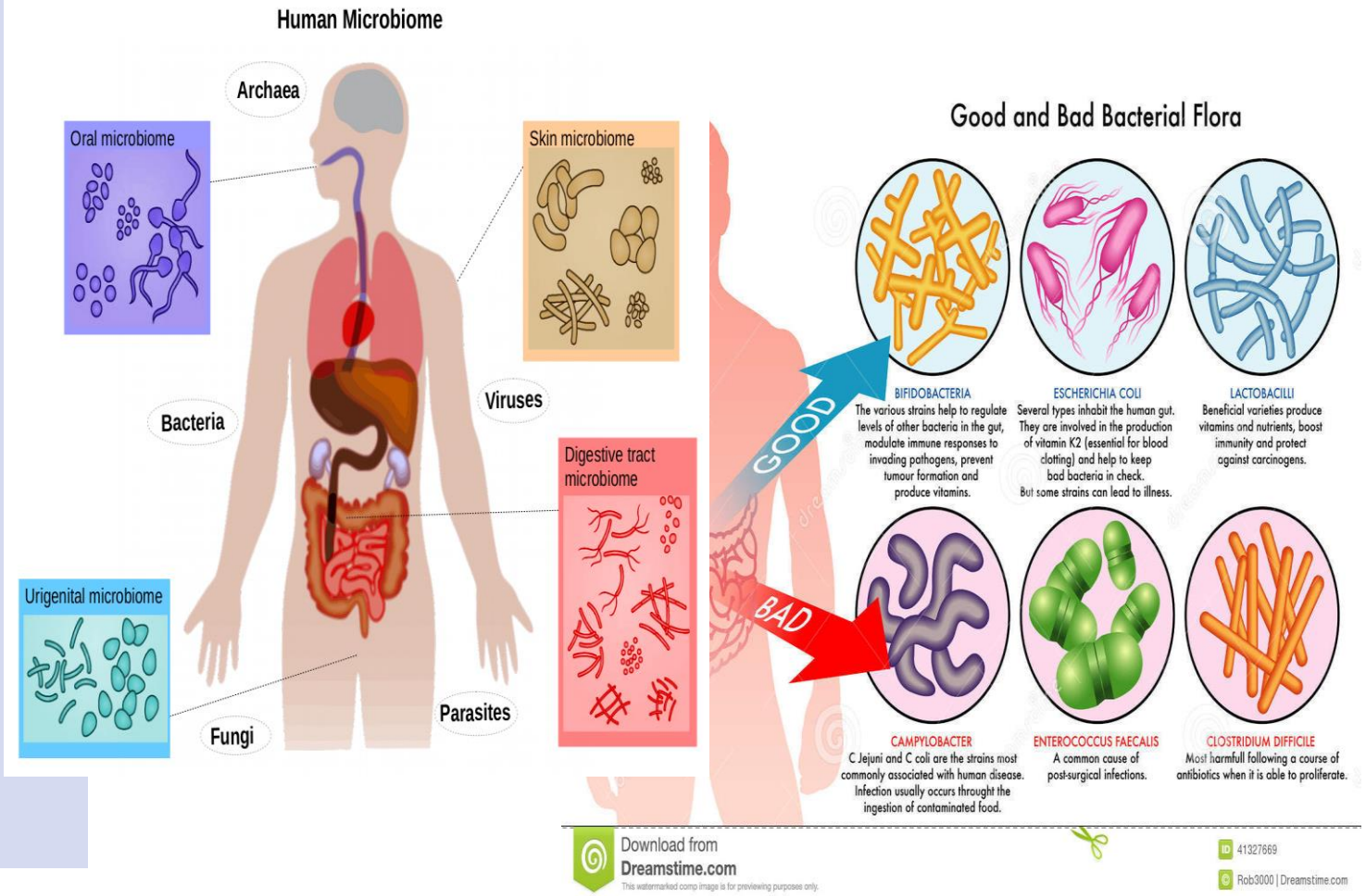
RASHT , TALAR SEPIDDAR

The body of a healthy individual is thought to contain approximately 3.8×10^{13} bacterial cells

Beyond Gut Feelings: how the gut microbiota regulates blood pressure
Nature Reviews Cardiology
Vol 15, January 2018





The etiology of SLE and LN is exceptionally complex and may be a result of the interaction between:

Genetic

- Genetically determined MBL2 deficiency was associated with development of LN in SLE patients.

- infections
- and
- Dysbiosis

- Hormonal changes in women is known that the microflora present in the genital tract changes with time..
- These differences may be caused by natural hormonal changes related to puberty and the
- beginning of menstruation.

- Other environmental factors: NSAID, PPi, Antibiotics.

Many of the known LN susceptibility genes are responsible for mediating inflammation via cytokine/chemokine production and the activation of myeloid and B cells . Some of the genes are related to bacterial responses, such as the mannose-binding lectin 2 (MBL2) gene. MBL recognizes carbohydrate patterns found on the surface of numerous pathogenic microorganisms, including bacteria. Binding MBL to a bacterial pattern results in the activation of the lectin pathway of the complement system.

Lupus Nephritis and Dysbiosis
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Dysfunction of:
controlling mechanisms (B cell, T helper, anti-inflammatory cytokines), anti-inflammatory cytokines and defensines secreted
by jejunal epithelial cells

Dysbiosis in LN

Immunodeficiency associated with SLE and cellular defects.

Environmental factors:
antibiotics , NSAIDs and PPi.

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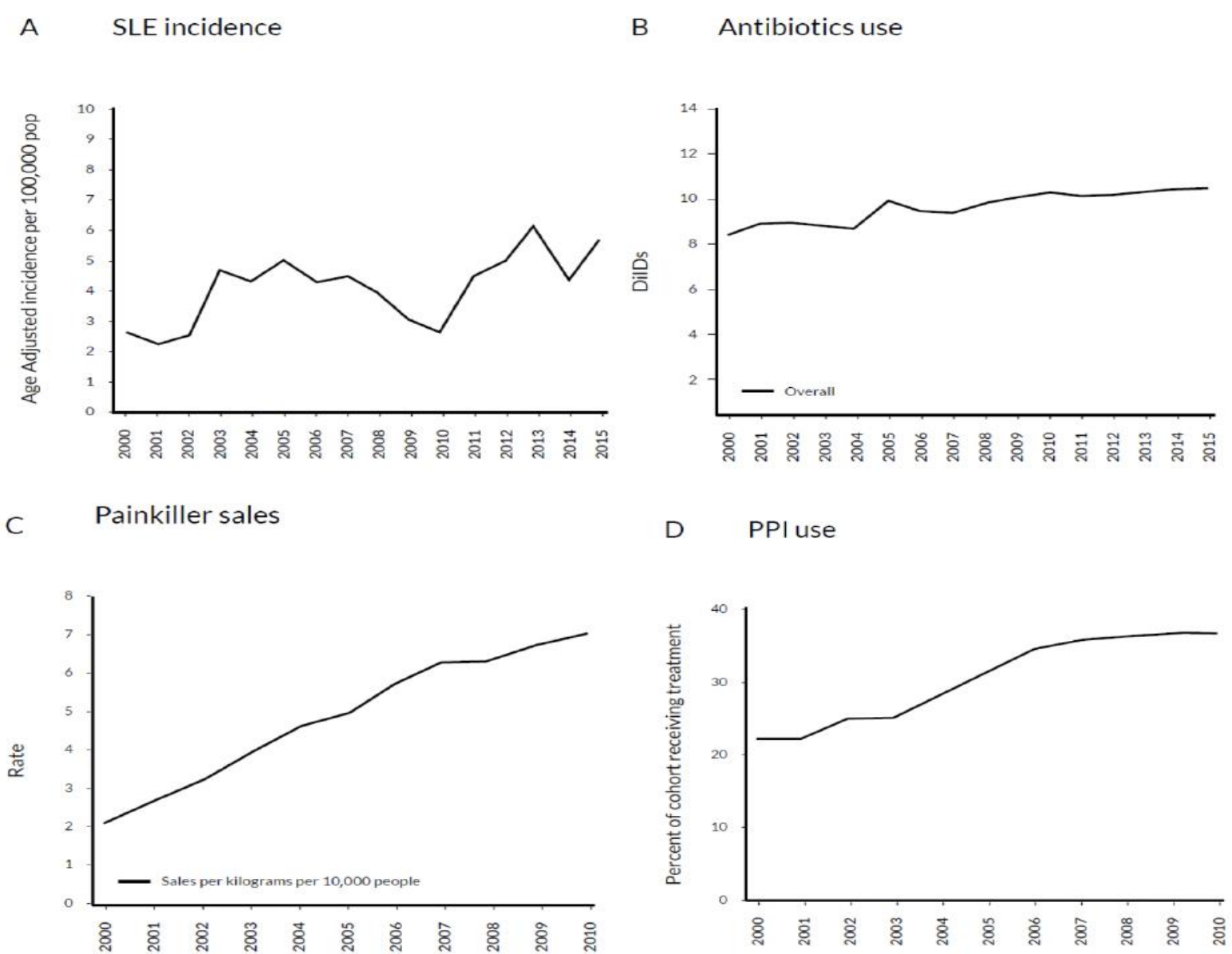


Figure 1. Similarities in trends of increased SLE incidence and consumption of antibiotics, nonsteroidal anti-inflammatory drugs and proton pump inhibitors in the years 2000–2015. (**A**)Age-adjusted systemic lupus erythematosus incidence per 100,000 population [10]. (**B**) Antibiotic consumption rate in daily doses [7]. (**C**) Nonsteroidal anti-inflammatory drug sales in kilograms per 10,000 people [8]. (**D**) Proton pump inhibitor consumption [9]. DDs—daily doses; DDD—defined daily dose; PPI—proton pump inhibitor.

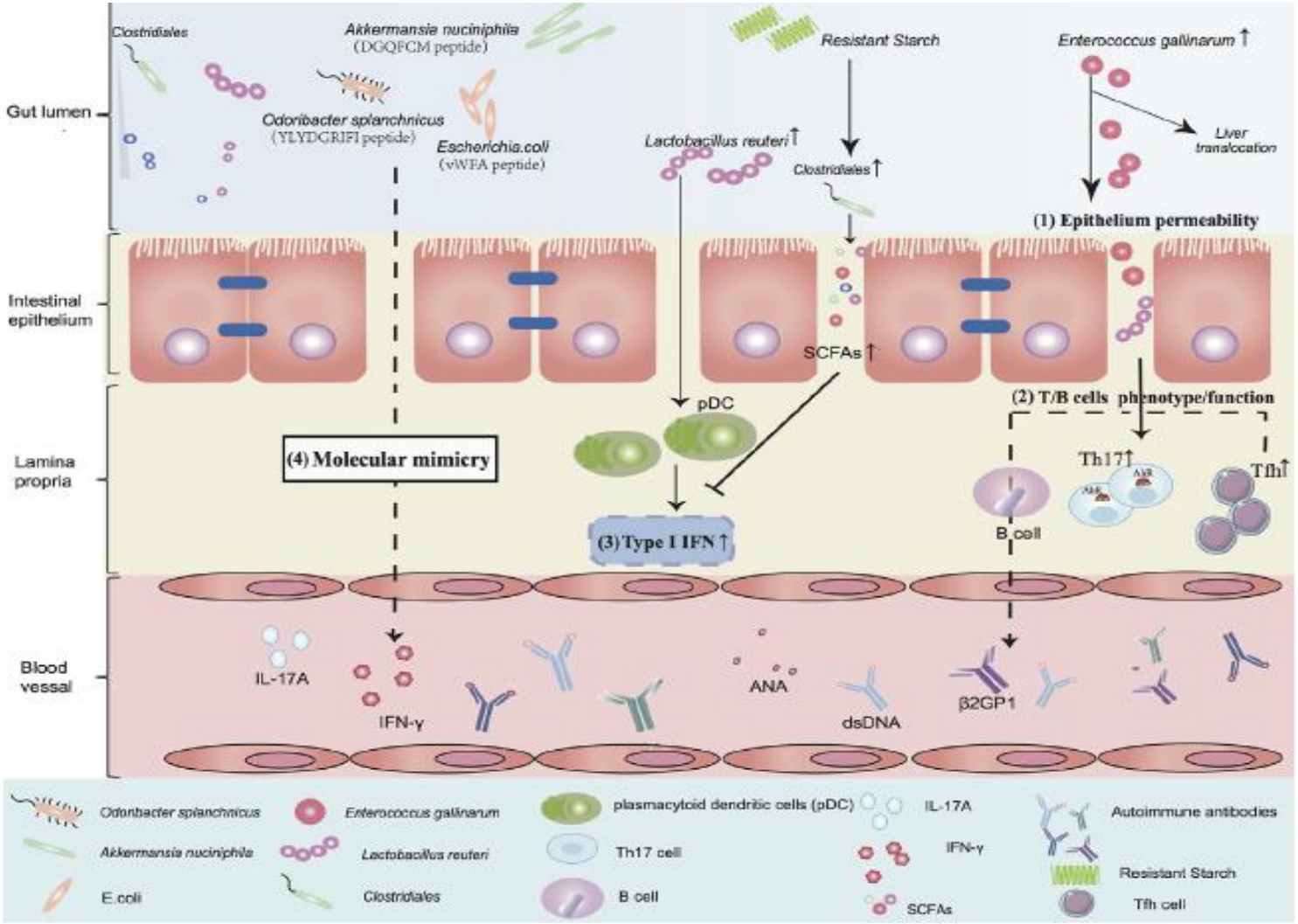


FIGURE 1 | An overview of the implication of gut microbiota in the aetiology of SLE. (1) Epithelium permeability: *Enterococcus gallinarum* induces an increase in epithelial permeability and translocates from the gut to the liver. (2) T/B cell phenotype/function: This triggers autoimmunity by upregulating the function of pDCs and Th17 cells and promotes the production of autoimmune antibodies such as dsDNA and β2GP1 in systemic circulation. (3) Type I IFN: *Lactobacillus reuteri* enriched in a lupus model can worsen autoimmune manifestations by engaging in type I interferon pathways. Dietary resistant starch feeding of mice increases *Clostridiales* abundance and promotes SCFA production to suppress type I IFN production. (4) Molecular mimicry: The peptide "YLYDGRIFI" of *Odoribacter splanchnicus* significantly increases IFN-γ and IL-17A expression in PBMCs of a subgroup of anti-Sm-positive SLE patients. The peptide "DGQFCM" from *Akkermansia nuciniphila* is capable of mimicking the extracellular part "DGQFCH" of human Fas and binds to IgG produced by memory B cells from SLE patients. Bacterial vWFA proteins expressed by *E. coli* can activate Ro60 reactive T cells.

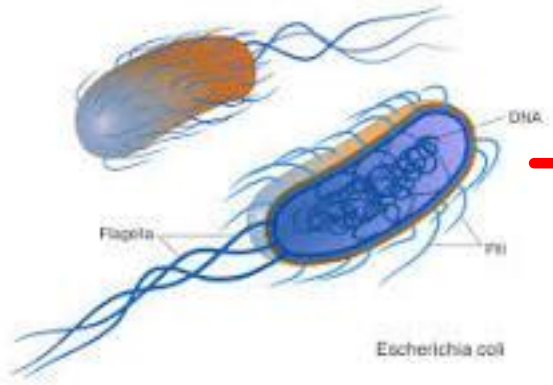
frontiers in Immunology
REVIEW

Gut Microbiome and Metabolites in Systemic Lupus Erythematosus: Link, Mechanisms and Intervention

Linghui Zhang[1†], Pingping Qing[1†], Heng Yang[1], Yongkang Wu[2], Yi Liu[1] and Yubin Luo[1*]

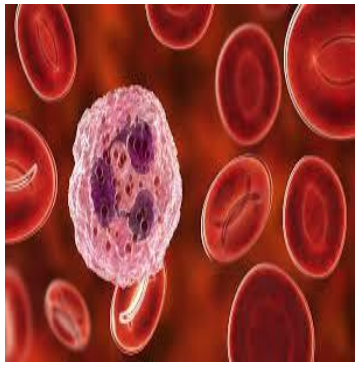
Molecular Mimicry

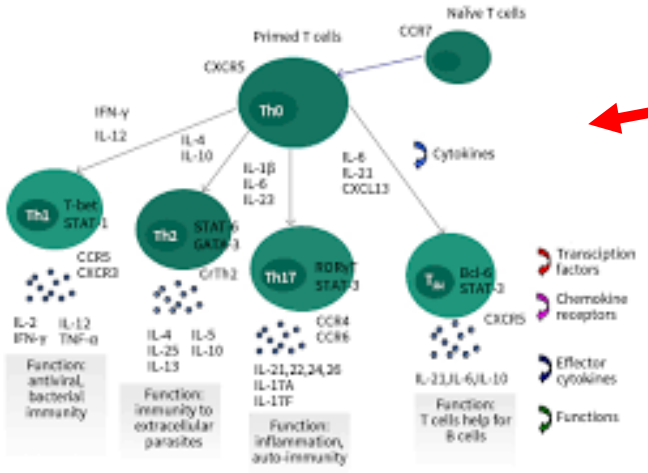
HLA-DR3



Secret metabolite that enter into blood

Peptide and glycoproteins mimic autoantigens and cause cross-reactivity.





Y. Schoenfeld et al., who found that mycobacterial cell wall glycolipids were associated with anti-dsDNA autoantibodies both in SLE patients and in mouse models.

Lupus ⟷ TB

For example, it has been shown that the YLYDGRIFI peptide of the IS66 family of Odoribacter splanchnicus transproteases can affect IFN- and interleukin 17A secretion from peripheral blood mononuclear cells in a subgroup of anti-Smith (Sm) antibody-positive SLE patients.

Zhang et al. reported that purified bacterial antigens of Burkholderia and transcriptional regulatory peptide referred to as RAGTDEGFG are able to bind to serum dsDNA antibodies in SLE patients. These findings may suggest that the formation of anti-dsDNA antibodies may involve molecular mimicry of Burkholderia.

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The cross-reactivity between Epstein–Barr virus nuclear antigen 1 (EBNA-1) and Ro60 proteins (The Ro/La system) has been suggested as a possible mechanism for the anti-Ro60 antibody response both in the rabbit model and in patients with SLE.

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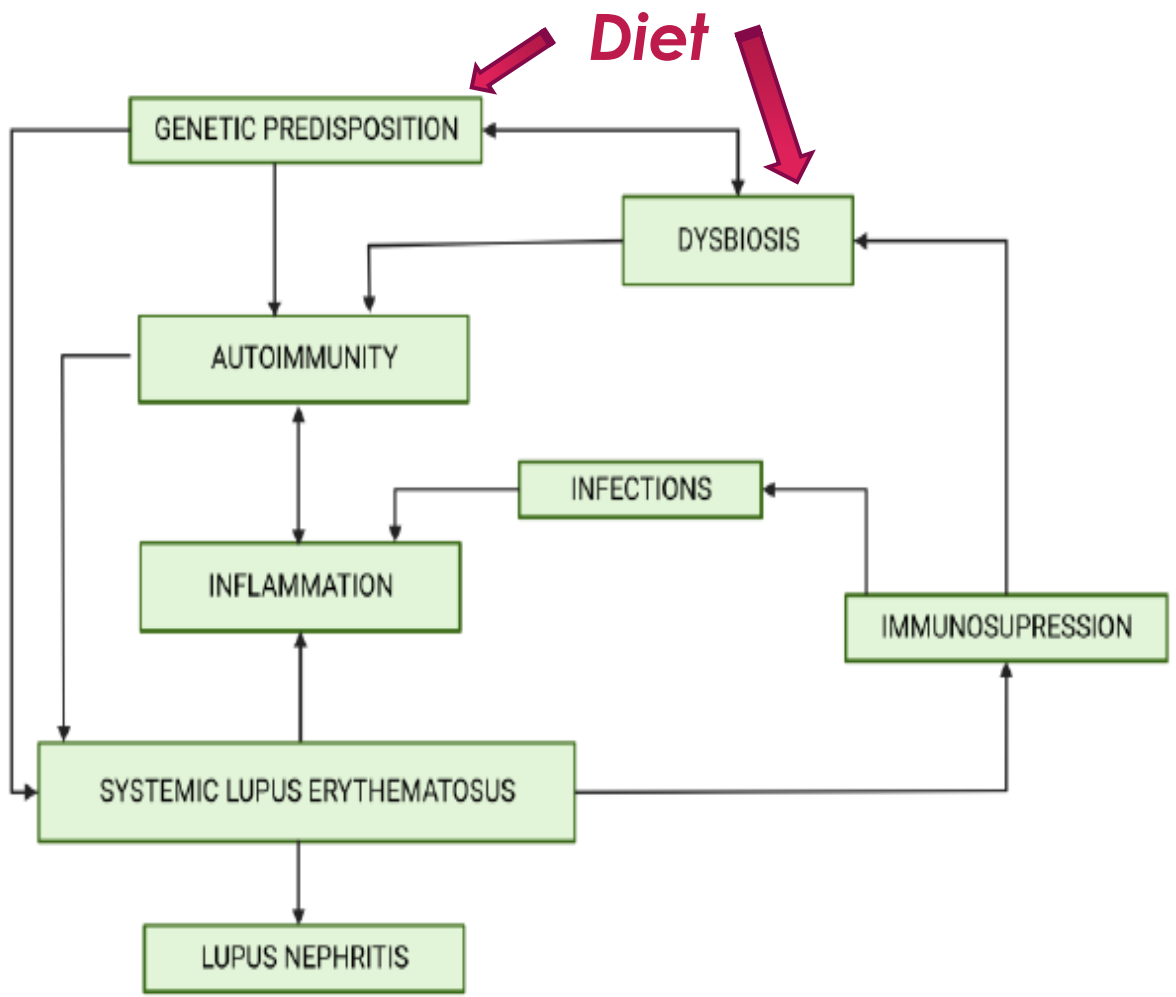

Figure 2. The associations between dysbiosis and factors involved in lupus nephritis development. Created by BioRender.com.

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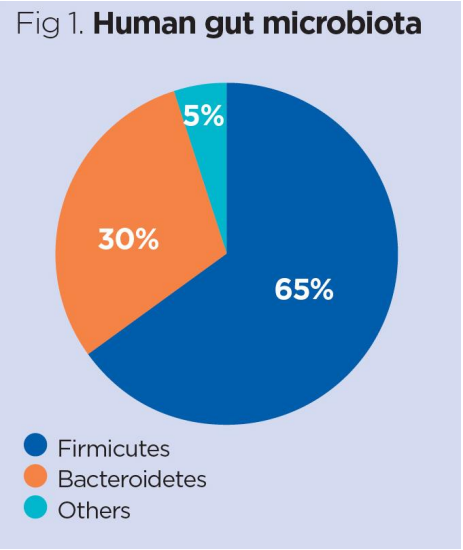
Microbiota, Dysbiosis and LN

Azzouz et al. have shown that SLE patients,
in contrast to healthy controls, presented with dysbiosis manifested as an over-abundance of anaerobic Ruminococcus gnavus (RG).
They demonstrated that anti-RG antibodies cross-react with anti-double-stranded DNA (dsDNA) IgG and patients with active classes III and IV LN have a higher level of anti-RG antibodies in their serum.
Taken together, these data highlight the association of microbiota, dysbiosis and LN.

Microbiota, Dysbiosis and LN (continued)

Hevia et al. observed a reduced Firmicutes/Bacteroidetes ratio, two species predominantly found in the gut microbiome, and a reduced abundance of Firmicutes phylum bacteria in patients diagnosed with SLE.



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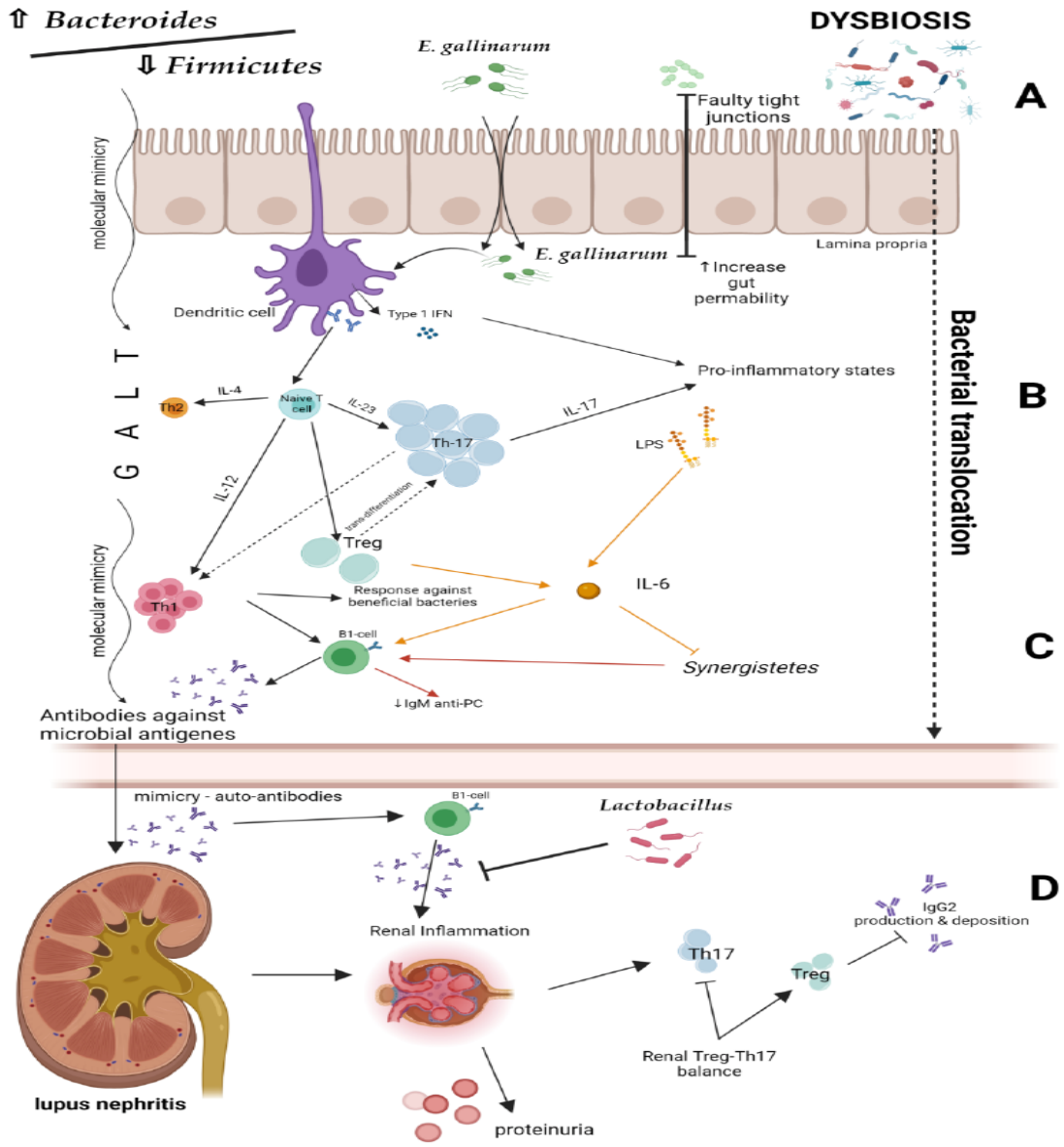


Figure 3. Potential mechanisms of lupus nephritis development [22,34,38,39]. Created by BioRender.com. (**A**) Intestinal barrier and bacterial translocation. (**B**,**C**) The inflammatory effects of dysbiosis. (**D**) Possible preventive role of probiotics in lupus nephritis development. IL—interleukin; IgG2—Immunoglobulin G2; Th—T helper; IgM anti-PC—Immunoglobulin M anti-phosphorylcholine; GALT—gut-associated lymphoid tissue.

Intestinal Permeability

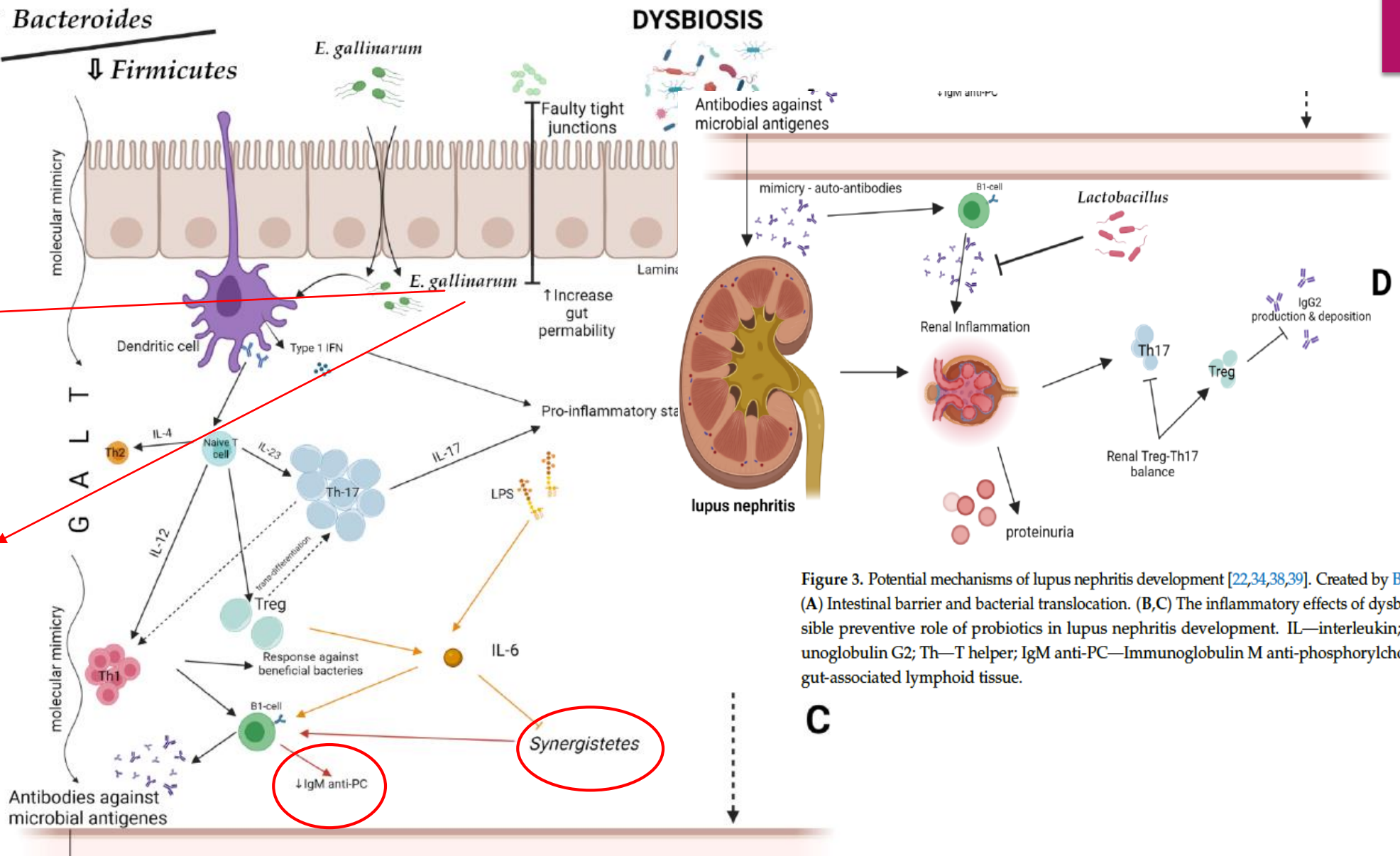
Intestinal ecosystem "leaky gut"

IS drugs

Liver

Type 1 IFN

Bacterial cell wall components, such as lipopolysaccharides, enter the systemic circulation, leading to inflammation



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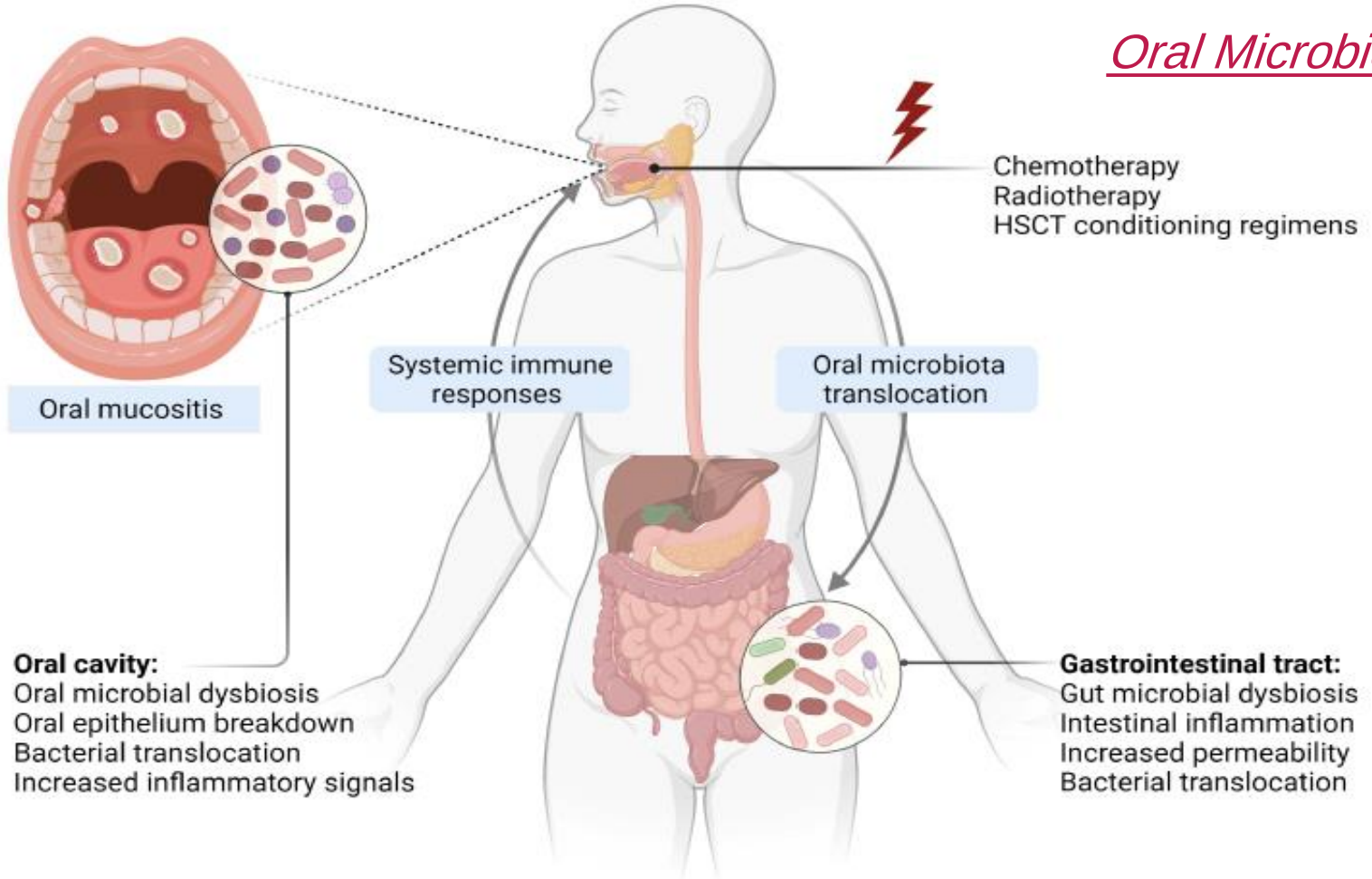
The oral cavity is an important reservoir of bacteria. However, its composition is highly variable, mainly due to exposure to numerous external and internal factors, such as smoking, food, poor hygiene, periodontitis, or salivary disorders.



OM= Oral Mucositis

FIGURE 1 | Oral-gut microbiome axis in the development of OM. Exposure to cytotoxic cancer treatments causes direct tissue injury and subsequent inflammatory responses leading to epithelial damage. Changes in the oral environment result in oral microbiota dysbiosis, which can cross through the damaged and ulcerated mucosa, interacting with immune cells and enhancing inflammatory responses. Intestinal pathological changes including gut microbiota dysbiosis, caused by anticancer agents and oral microbiota translocation into the gut, disrupt intestinal homeostasis and facilitate bacterial translocation into circulation and activation of systemic immune responses, which in turn aggravate OM severity (Created with Biorender.com).

Oral-Gut Microbiome Axis in the Pathogenesis of Cancer Treatment-Induced Oral Mucositis
Frontiers in Oral Health
March 2022 | Volume 3 | Article 881949

Correa et al. showed that the oral flora in SLE patients is significantly different from flora in healthy individuals.

Periodontitis is also much more common in patients with SLE.

The authors suggested that subgingival bacterial species associated with SLE have a significant impact on the host systemic cytokine system, influencing general condition.

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Genital Microbiota

Although lupus affects women significantly more often than men, there are not many studies linking its development to uro-genital dysbiosis or infections.

Microflora present in the genital tract changes with time:

- ✓ Natural hormonal changes related to puberty
- ✓ Menstruation
- ✓ Sexual activity

These are constantly modified throughout a woman's life until menopause.

The vaginal dysbiosis in SLE patients may be influenced both by the disease and by its treatment.

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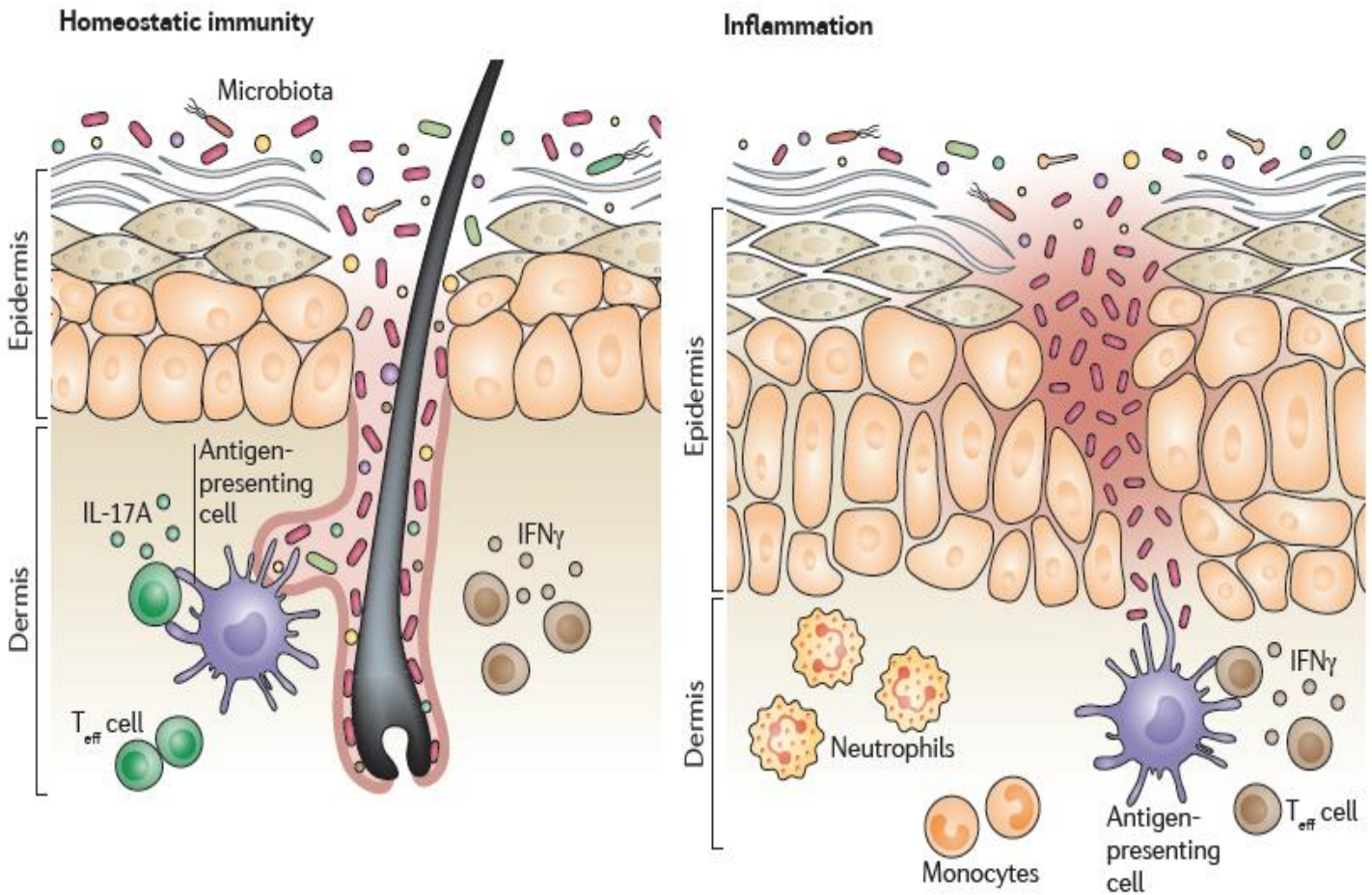
Crosstalk between the immune system and the skin microbiota
Cutaneous commensals are essential for education of the immune system.
different microorganisms have been shown to elicit distinct effects on the immune system.

under steady-state conditions, induction of effector T (Teff) cells in response to skin microorganisms occurs in the absence of classical inflammation in a process termed 'homeostatic immunity'

Skin Microbiota



Zhou et al. revealed that the skin microflora of SLE patients presents significant differences when compared to healthy controls.

a comparison between remission and active SLE groups revealed that the family Caulobacteraceae was positively correlated with SLE disease activity index (SLEDAI) and negatively with C3.

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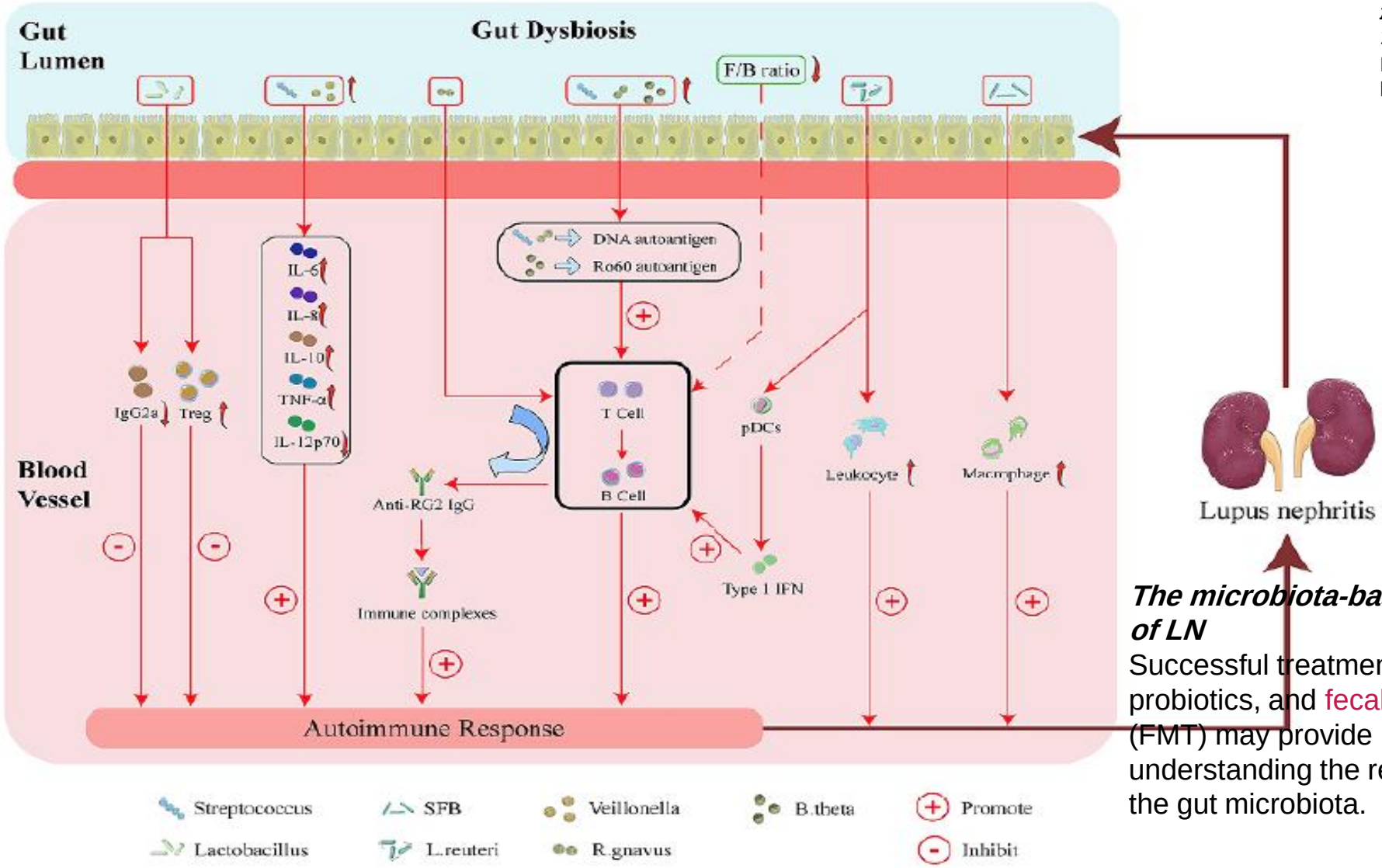
Alterations of the gut microbiota in the lupus nephritis: a systematic review
Renal Failure 2023, VOL. 45, NO. 2, 2285877
https://doi.org/10.1080/0886022X.2023.2285877



The microbiota-based therapeutic prospects of LN

Successful treatment of LN through diet, probiotics, and fecal microbiota transplantation (FMT) may provide new evidence for understanding the relationship between LN and the gut microbiota.

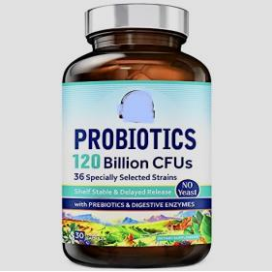
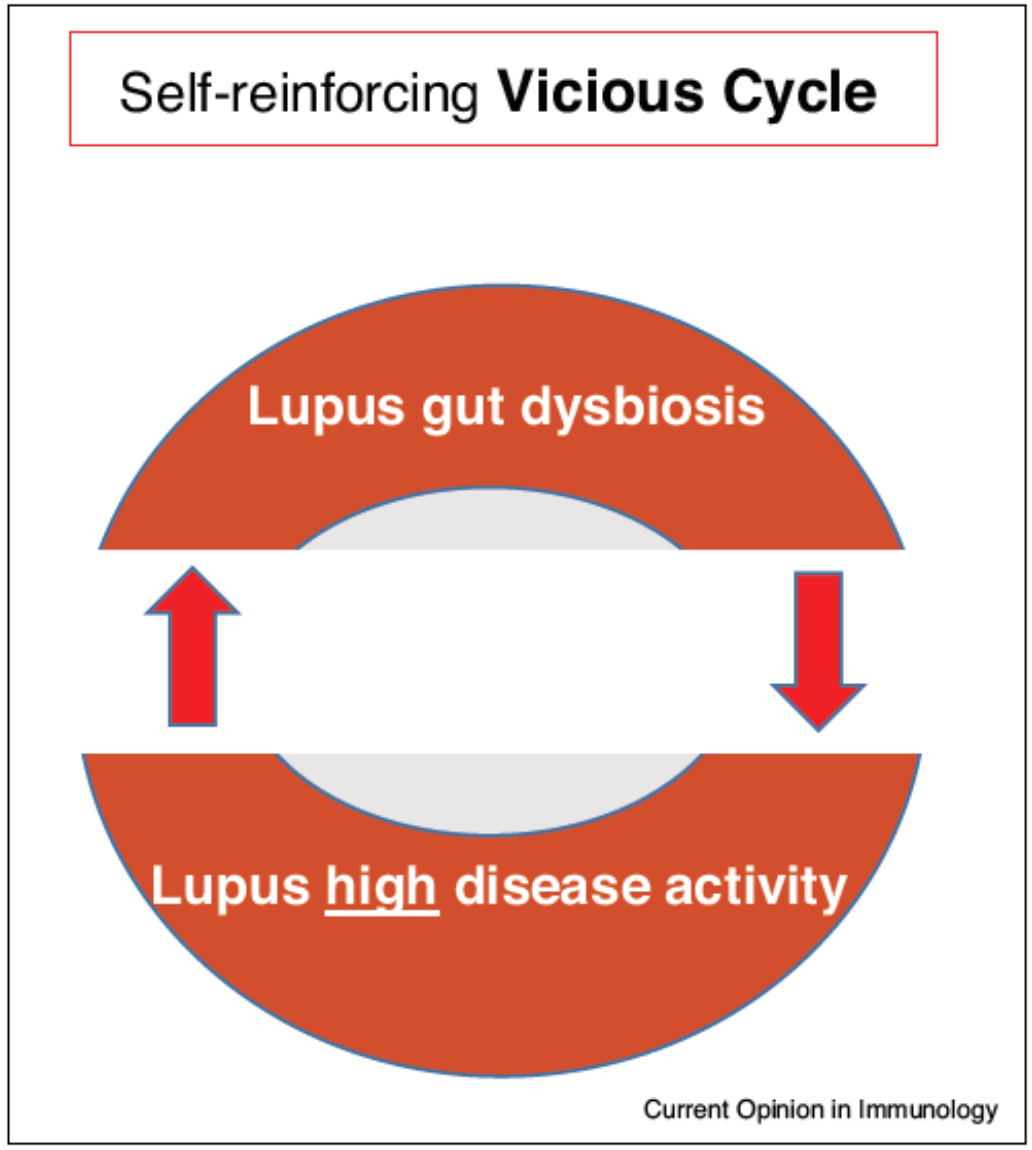


Figure 3. Possible mechanism linking gut microbiota dysbiosis to LN. Alteration of specific microbial taxa may contribute to the pathogenesis and progression of LN through the following four factors. First, the alteration of specific microbial taxa can induce LN by promoting kidney M2-like macrophage infiltration and leukocyte recruitment. Second, the gut microbiota may contribute to LN by enhancing the autoimmune response. Third, *Streptococcus* combined with *Veillonella* can enhance the autoimmune response, including by increasing IL-6, IL-8, IL-10, and TNF-α levels, whereas decreased IL-12p70 may induce LN. Fourth, the alteration of specific microbial taxa can increase the abundance of Tregs, while the decrease in the deposition of IgG2a may alleviate LN. *SFB, Segmented Filamentous Bacteria. L. reuteri, Lactobacillus reuteri. R. gnavus, Ruminococcus gnavus. B. theta, Bacteroides thetaiotaomicron.* F/B, *Firmicutes/Bacteroidetes.* pDCs, plasmacytoid dendritic cells. IL-12p70, interleukin-12p70. IL-10, interleukin-10. IL-8, interleukin-8. IL-6, interleukin-6. TNF-α, tumor necrosis factor α. Tregs, regulatory T cells. LN, lupus nephritis.



The influences of Lupus disease activity and Gut dysbiosis may be bidirectional. Stabilization of a dysbiotic gut microbiome community may be an adaptation to a local gut environment arising from Lupus pathology, which had expansions and contractions of specific taxa that directly or indirectly drivers of Lupus pathogenesis.

Systemic Lupus Erythematosus and dysbiosis in the microbiome: cause or effect or both?
Current Opinion in Immunology 2019, 61:80–85


سپاس بسیار

Skin Microbiota

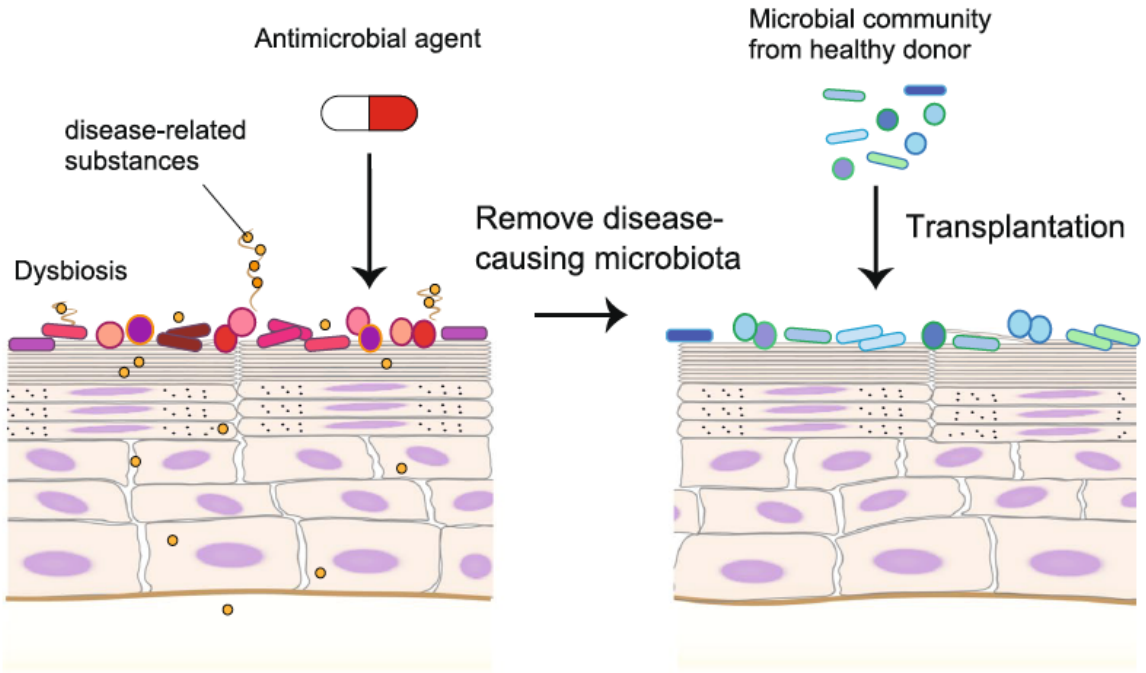


Fig. 2 Transplantation of skin microbial community. One therapeutic strategy using live bacteria for skin diseases is transplantation of the whole skin microbial community from healthy donors to diseased skin associated with dysbiosis, such as patients with malodor. Pre-colonized disease-causing skin microbiota are removed by antibacterial agents such as antibiotics. Subsequently, the microbial community collected from the skin of non-odorous donors is transplanted to the patient's skin to occupy space and provide nutrition, preventing other bacteria from colonizing the skin niche and producing disease-causing substances

Skin Microbiota

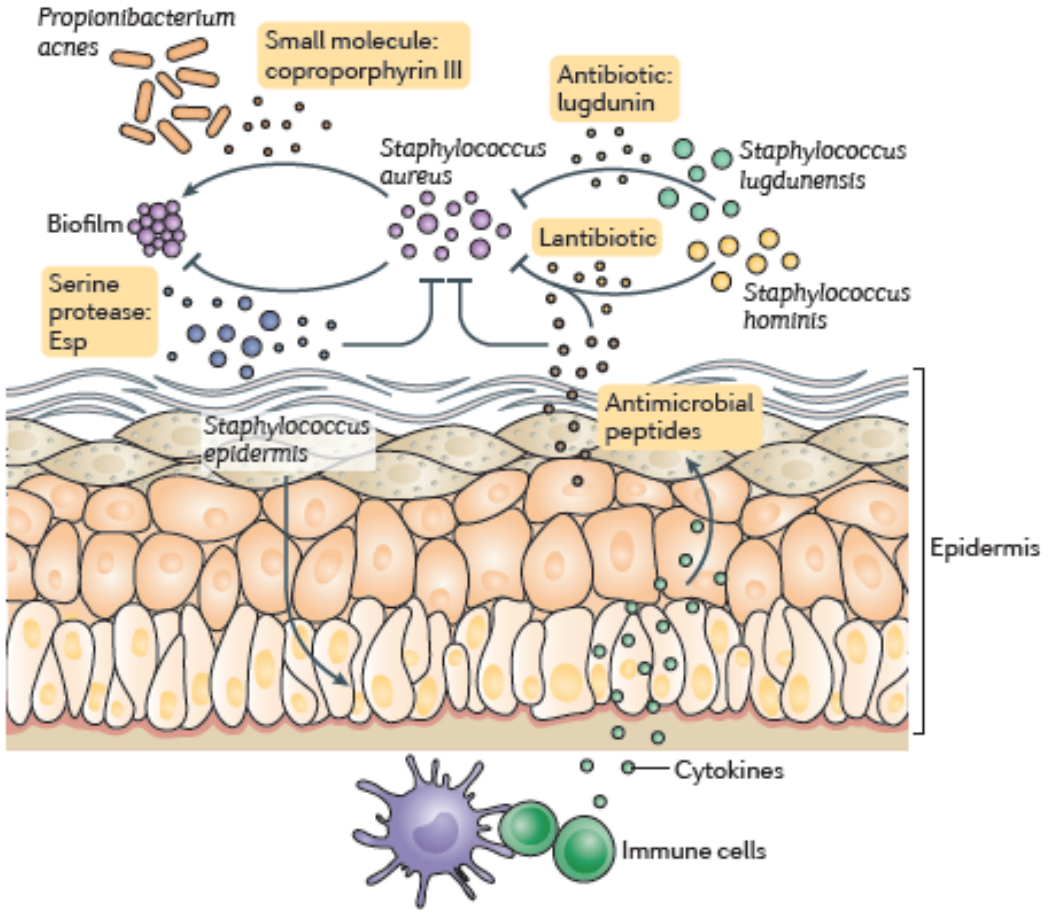


Figure 3 | **Skin commensal interactions with *Staphylococcus aureus*.** Skin microbial communities are shaped by interactions between organisms and with the host. In the skin, many interactions between commensals and *Staphylococcus aureus* have been identified. Antibiotics produced by coagulase-negative *Staphylococcus* and specifically by *Staphylococcus lugdunensis* prohibit colonization of *S. aureus*. Also, *Staphylococcus epidermidis* can inhibit *S. aureus* biofilm formation with production of the serine protease glutamyl endopeptidase (Esp). Moreover, when Esp-expressing *S. epidermidis* induces keratinocytes to produce antimicrobial peptides via immune cell signalling, *S. aureus* is effectively killed. In addition, *Staphylococcus hominis*-produced lantibiotics synergize with human antimicrobial peptide LL-37 to decrease *S. aureus* colonization. In contrast to inhibiting *S. aureus*, *Propionibacterium acnes* produces a small molecule, coproporphyrin III, that promotes *S. aureus* aggregation and biofilm formation.