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Editorial

Alterations of Plasma Microbiome: A Potentially New Perspective to the Dysbiosis in Systemic Lupus Erythematosus?

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The human microbiome, which consists of the microbial communities inhabiting the human body, has sparked growing excitement in both basic research and clinical practice.[1,2] Gut microbiota, in particular, has been considered a major environmental factor in modulating immune responses in autoimmune diseases (ADs).[3,4] Systemic lupus erythematosus (SLE) is a prototype AD characterized by dysregulation of both innate and adaptive immune responses, autoantibody production, multiorgan involvement, and upregulation of interferon-stimulated genes.[5,6,7] The etiology of SLE remains unclear but is partially attributed to a combination of genetic and environmental factors.

As a critical environmental factor, dysbiosis is linked to SLE immunopathogenesis.[3,4,8,9,10,11] Patients with SLE displayed decreased richness and diversity of gut microbiota compared to controls.[8,9,10,11] Further, a significantly lower ratio of Firmicutes to Bacteroidetes in patients with SLE was reported in several studies.[3] The implication of gut dysbiosis in SLE pathogenesis was further corroborated by the findings that cecal microbiota transfer from SLE-prone mice induced autoimmune phenotypes in germ-free congenic C57BL/6 mice.[12] With the introduction of metagenomics and metabolomics, a more complicated interaction between host and gut microbiome has been revealed in SLE.[8,9] We recently identified 2 autoantigen cross-reacting peptides from SLE-enriched species in the gut with the ability to promote the production of inflammatory cytokines.[8] Of interest, the gut microbiome also helps reveal novel relationships among complex human diseases. A recent study found that SLE and chronic myeloid leukemia shared some common gut microbiome features, suggesting that different complex diseases may be mechanistically correlated by sharing certain common gut microbiome features.[13]

In addition to alterations in gut microbiota, oral and skin dysbiosis have been described in patients with SLE.[11,14,15] For example, patients with SLE exhibited a dysbiotic subgingival microbiota characterized by higher subgingival bacterial load, reduced microbial diversity, and changes in bacterial composition with enrichment of pathogenic bacteria in comparison to controls.[14] Further, the cutaneous microbiome of patients with SLE displayed decreased diversity in community richness and evenness compared to healthy controls (HCs).[15] Additionally, the skin dysbiosis was correlated with clinical features of SLE, such as lower complement levels and renal involvement,[15] suggesting skin dysbiosis may also be implicated in the pathogenesis of SLE.

Traditionally, blood has been regarded as a sterile environment, and the presence of microbes was considered an indication of infection. However, this concept has been challenged by the findings of the existence of a "healthy" human blood microbiome through the application of next-generation sequencing of the 16S rRNA gene.[16] In this issue of *The Journal of Rheumatology*, James and colleagues examined the microbiome composition of the paired plasma and gut in a small cohort of female patients with SLE and HCs.[17] They found that the plasma microbial alpha diversity was significantly decreased in patients with SLE and that the beta diversity also displayed marginal differences in patients with SLE compared to HCs. In contrast, they failed to identify any alterations of the microbial alpha and beta diversities in gut microbiome between patients with SLE and HCs. While this study inevitably had several limitations, including small sample size, female sex only, and low SLE Disease Activity

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Index (SLEDAI) score as well as low taxonomic resolution, the findings of this study along with their previous observations[18] may shed novel insights into SLE pathophysiology.

One major question this study asked was whether the plasma microbiome represents the microbial community in the gut. They found that the microbial composition in plasma differed significantly from that of their corresponding gut counterpart in both patients with SLE and HCs, indicating that the plasma microbiome may represent a distinct community different from the gut microbiome in a disease-independent manner. Currently, it remains to be determined to what extent these microbes represent the living microbes, as the detection of fragments of bacterial DNA in the blood does not necessarily represent the presence of living bacteria. Even if they are living bacteria, it remains unclear whether the plasma microbiome represents a unique ecological niche or these bacteria are transient blood residents. Some studies have suggested that the plasma microbiome may be derived from bacteria translocation from the intestinal tract, whereas others have shown that the blood microbiome closely resembles the skin and oral microbiomes.[16] Therefore, analysis of skin, oral, and gut microbiomes should be performed along with that of blood samples to enable a better understanding of the potential origin of these microbes.

Another important aspect that needs further investigation is the functional and clinical relevance of the plasma microbiome in SLE. Gut dysbiosis has been suggested to promote autoimmunity through molecular mimicry, bystander activation, and skewing the proinflammatory/antiinflammatory balance.[3,4] It thus remains to be defined whether plasma dysbiosis is also implicated in the pathogenesis of SLE or it is simply a bystander reflecting disease state. For instance, lipopolysaccharide (LPS), a major component of the outer membrane of Gram-negative bacteria, plays a crucial role in promoting inflammation and other SLE-related comorbidities such as cardiovascular disease. In fact, patients with SLE displayed elevated levels of circulating LPS.[18] Utilizing the metagenomic analysis, we have also demonstrated that the biosynthesis of O-antigen, the outermost domain of LPS, was increased in patients with SLE and decreased after treatment.[8] The impaired gut barrier in SLE that enables the translocation of bacteria from the gut to the circulation has been considered to contribute to the increased levels of circulating LPS. It would be interesting to determine whether plasma dysbiosis also contributes to the circulating LPS pool. In addition, it is important to dissect where the blood microbiome lies in the complex network that predisposes an individual to SLE, as well as the relative amount of contribution to the disease pathogenesis in comparison to other variables such as gut microbiome.

One of major characteristics of gut dysbiosis is the decrease in alpha diversity. Several studies reported significant decrease in alpha diversity in SLE gut microbiome,[8,9,10] whereas others did not observe such differences.[19] The findings by James and colleagues also failed to identify differences in alpha diversity in the plasma microbiome between patients with SLE and HCs,[17] possibly due to the small sample size. However, even with such a small cohort, the authors found significant differences in the plasma microbiome between patients with SLE and HCs, suggesting that the blood microbiome may be a more sensitive indicator of dysbiosis than the gut microbiome. Of interest, their previous results showed that first-degree relatives of patients with SLE also displayed a reduction in diversity compared to unrelated HCs, whereas patients with SLE receiving treatment had a circulating microbiome profile with a diversity similar to that in HCs.[18] While it remains unclear whether the gut microbiota of first-degree relatives of patients with SLE also differ from unrelated HCs, plasma microbiota provide a novel approach in understanding dysbiosis in SLE.

The gut microbiome can be affected by a number of factors, such as diet, genetics, age, and lifestyle.[1] It is unclear whether the plasma microbiome is also affected by these factors. Azzouz et al have shown that the gut microbiome of SLE patients with higher SLEDAI scores had greater restrictions in taxonomic diversity.[10] They further showed that *Ruminococcus gnavus*, an obligate anaerobic species in the fecal communities, was preferentially expanded in patients with SLE, especially in those with high disease activity and lupus nephritis.[10] It remains to be determined whether certain bacteria were preferentially enriched in plasma in SLE and whether their enrichments associate with disease activity and organ involvement. In addition, we previously showed that the posttreatment gut microbial composition in patients with SLE was more similar to that in HCs, suggesting that a recovery of gut microbiota is linked with disease improvement.[8] It would be interesting to determine whether plasma dysbiosis can also be corrected by treatments and restored along with disease alleviation. It has been reported that patients with primary Sjögren syndrome (pSS) and with SLE share similar alterations in gut microbiota composition that can distinguish them from healthy individuals, whereas oral microbiota composition shows disease-specific differences between patients with pSS and SLE.[11] It would also be interesting to see whether the plasma microbiota profile is SLE-specific or is a shared profile with other ADs.

The identification of plasma microbiome alterations sheds novel insights into SLE dysbiosis. As results from James and colleagues have suggested that plasma dysbiosis may be more sensitive than gut dysbiosis,[17] a specific plasma microbiome–based signature may have diagnostic and prognostic potential in SLE. Further studies with larger cohorts and diverse populations will be needed for an in-depth understanding of how plasma dysbiosis is implicated in the pathogenesis of SLE, if at all. Overall, this study,[17] despite several limitations, introduces plasma dysbiosis as a potentially significant new member of the dysbiosis family in SLE. Systematic analysis of plasma dysbiosis may fuel the process of precision medicine and individualized treatment.

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