Disturbed gut virome with potent interferonogenic property in systemic lupus erythematosus

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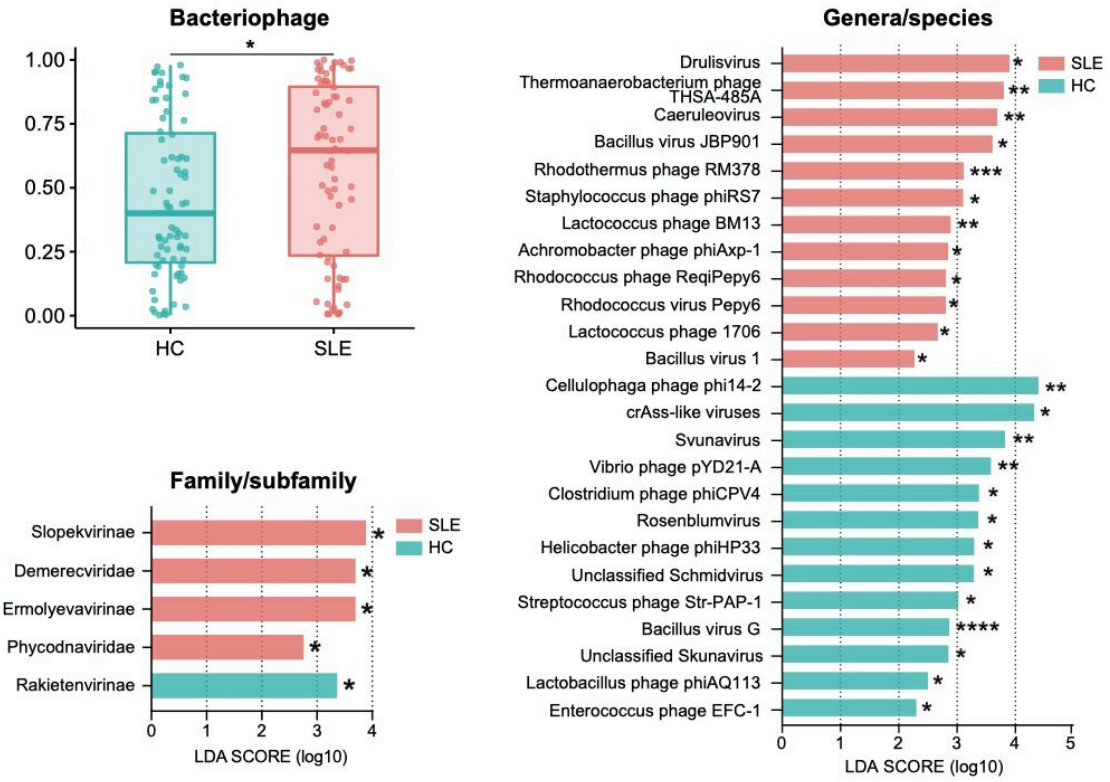

The taxonomic profile and the interferon-α-stimulatory capacity of gut virus-like particles in patients with systemic lupus erythematosus. Credit: Science China Press

Systemic lupus erythematosus (SLE) is a prototypical autoimmune disease that can affect multiple tissues and organs. Common manifestations of SLE include fever, fatigue, malar rash, oral ulcer, alopecia, arthritis, and nephritis. Women of childbearing age are most likely to suffer from SLE. Currently, there is no cure for SLE, and it lacks an effective and safe treatment regimen because its underlying etiopathogenesis remains elusive.

The gut microbiota refers to the microbial community that distributes along the mucosal surface of gastrointestinal tract. The gut microbes participate in the development and function of host immune system. Disturbed gut microbiota has been associated with the pathogenesis of autoimmune diseases like SLE. However, given the technical limitations, previous studies mostly focused on the abundant gut bacteria, while the gut virome of SLE patients remains under-explored.

A study led by Prof. Xuan Zhang (Beijing Hospital) and Prof. Jun Wang (Chinese Academy of Sciences) recruited 76 SLE patients and 75 matched healthy participants, and collected their feces. The SLE patients were mostly treatment-naive and had not taken any corticosteroids, immunosuppressants, or anti-malarials for the preceding 3 months. Human cells and bacterial cells were removed from the feces and free virus-like particles (VLPs) were enriched by ultracentrifugation. Then, viral nucleic acids were extracted and profiled by shotgun sequencing.

The work is published in the journal *Science Bulletin*.

The community richness, evenness, and distribution of gut VLPs were not significantly different between SLE patients and healthy participants. However, the proportion of bacteriophages, the virus that infects bacteria instead of human cells, was significantly higher in SLE patients compared to healthy participants.

As regards the differentially abundant viral genera and species, the most discriminating ones in SLE patients were Drulisvirus, Thermoanaerobacterium phage THSA-485A, Caeruleovirus, and Bacillus virus JBP901, whereas the predominant ones for HCs were crAss-like viruses and one of their species, Cellulophaga phage phi14:2.

Interestingly, the gut abundance of SLE-enriched Staphylococcus phage phiRS7 was positively associated with SLE disease activity index as well as the levels of inflammatory indicators, including C-reactive protein and erythrocyte sedimentation rate.

The intercorrelations between gut virome and bacteriome were also analyzed. Using the Procrustes analysis, a significant transkingdom association between the viral and bacterial community in the gut microbiota was found. In addition, some of the bacteriophages co-varied with bacterial genera that were not their hosts, suggesting a complicated interplay between the gut virome and bacteriome.

Diagnostic models based on differentially abundant viruses and bacteria using a random forest algorithm were constructed. The combination of gut viral and bacterial markers displayed better performance (area under the curve = 0.948) than using data from one kingdom alone in distinguishing SLE patients from healthy participants.

Finally, VLPs were isolated from feces and added to the culture of human cells. VLPs from non-treated SLE patients promoted the transcription and production of interferon-α, a pivotal pathogenic factor in SLE, in both Caco cells (an epithelial cell line) and immune cells separated from human blood compared to VLPs from healthy people. Intriguingly, the interferon-stimulatory capacity diminished in VLPs from post-treated SLE patients.

In summary, this is the first VLP profiling of the gut virome in SLE

patients that revealed the viral signatures in the gut microbiota of SLE patients. It also shed novel insights into SLE pathogenesis by connecting the SLE-related gut virome with the promoted production of interferon-α.

More information: Beidi Chen et al, Disturbed gut virome with potent interferonogenic property in systemic lupus erythematosus, *Science Bulletin* (2023). DOI: 10.1016/j.scib.2023.01.021

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