

Multomics-guided discovery of protective microbiome signatures in lupus-prone mice treated with *Faecalibacterium prausnitzii*

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Gut microbiome dysbiosis has been implicated in the pathogenesis of systemic lupus erythematosus (SLE). However, microbiota-targeted therapeutic strategies have been lacking. Here, we report the potential of *Faecalibacterium prausnitzii* (strain UT1) to ameliorate gut dysbiosis and alleviate disease progression in the B6.*Sle1*.Yaa male mouse model of SLE. Fecal metagenomes of patients with SLE shifted carbohydrate catabolism from dietary fibers to host glycans, coinciding with depletion of *F. prausnitzii*. Oral administration of UT1 partially reversed lupus-associated microbiome alterations and rescued carbohydrate metabolic deficiency in lupus-prone mice. Using correlative metatranscriptomics and metabolomics, we observed restricted expression of bacterial genes related to mucin degradation, elevated pentose phosphate pathway and bile acid-modifying activities, and redirected tryptophan catabolism toward indoleacetic and indoleacrylic acids. Further host cell profiling showed that UT1 rebalanced colonic regulatory T (Treg) and T helper 17 (Th17) cell responses, suppressed systemic autoimmune activation and autoantibody production, and reduced renal pathology. Thus, our findings identify SLE-associated active microbiome signatures and provide a probiotic candidate for the treatment of lupus disease.

Gut microbiota dysbiosis has been linked to the pathogenesis of systemic lupus erythematosus (SLE), characterized by a loss of immune tolerance and overactivation of the immune system, leading to the production of autoantibodies against nuclear components^{1,2}. The gut microbiome in autoimmune diseases exhibits significant instability and interindividual variations that affect the course of disease and clinical manifestations³. As such, metagenomics analyses of fecal samples have been conducted in animals and humans to compare the abundance and distribution of microbial taxa associated with SLE and understand their potential contribution to pathogenesis^{4–6}. Yet very little information is available regarding the transcriptional activity of

the dysbiotic microbiome. The metatranscriptome, composed of actively expressed microbial transcripts under a specific environmental condition⁷, provides a link between the metagenome and community phenotypes that is crucial for understanding the functional ecology of the microbiome.

Emerging data have uncovered the roles of specific bacterial species in immune activation and disease severity in SLE. The opportunistic pathogen *Enterococcus gallinarum* is found in the stools and liver of a small subset of SLE patients⁸. In lupus-prone mice, *E. gallinarum* can translocate to the mesenteric lymph node, liver, and spleen, promoting T helper 17 (Th17) cell

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and autoantibody responses^{8,9}. Interestingly, the genome of *E. gallinarum* isolated from the liver differs from that of fecal strains in genes regulating transcription, nutrient use, or environmental sensing. This suggests that pathobiont evolution within the host may facilitate bacterial translocation and pathogenesis¹⁰. Additionally, *Lactobacillus reuteri*, enriched in the stools of some SLE patients, also translocates to extraintestinal organs where it stimulates plasmacytoid dendritic cells and type I interferon (IFN-I) response in a mouse model of SLE¹¹. Moreover, the intestinal expansion of *Ruminococcus gnavus* has been observed in patients with active lupus nephritis, and the abundance of *R. gnavus* correlates with the clinical disease activity¹². These nephritic patients produce antibodies to *R. gnavus* lipoglycan up to 1000-fold higher than healthy individuals, hinting at an important involvement of the lipoglycan in modifying host immune responses^{12,13}.

While providing substantial mechanistic insights into microbiome-associated SLE pathogenesis, these studies have been focused on individual pathobionts with little consideration of the corresponding commensal microorganisms, which are almost always contracted during pathobiont expansion^{5,6,12}. For instance, the recent metagenomic analysis of a large cohort of SLE patients revealed a significant reduction of *Faecalibacterium prausnitzii* compared to healthy controls⁶. In patients with active lupus nephritis, the abundance of *F. prausnitzii* is also concurrently reduced with the bloom of *R. gnavus*¹². However, whether *F. prausnitzii* plays a protective role against SLE remains unexplored.

F. prausnitzii is one of the most abundant obligate anaerobes and the major butyrate producer in the human gut microbiota¹⁴. A reduced abundance of *F. prausnitzii* is associated with a higher risk of several human intestinal diseases, such as inflammatory bowel diseases^{15–17} and extraintestinal disorders, including Parkinson's and Alzheimer's diseases^{18,19}. Oral supplementation of *F. prausnitzii* or bacterial culture supernatants has been shown to mitigate inflammatory responses^{20–22} and reduce the frequencies of IL-17-producing cells in an experimental mouse model of rheumatoid arthritis²³. Interestingly, certain strains of *F. prausnitzii* encode a fatty acid amide hydrolase that hydrolyzes a variety of N-acylamides, including oleoylethanolamide, a satiety factor that suppresses appetite in undernourished children²⁴. We recently demonstrated that *F. prausnitzii* strain UT1 (abbreviated as UT1 hereafter), which belongs to the most prevalent phylogenetic clade of *Faecalibacterium* complex in the global human population^{25,26}, modifies the gut microbiome structure and composition and supports the carbohydrate catabolic function of the gut microbiome in C57BL/6 (B6) non-autoimmune mice. UT1 also restricts the abundance of mucin-degrading carbohydrate-active enzymes (CAZymes) and mucin-derived glycans critical for intestinal barrier function²⁵. Given the pivotal role of *F. prausnitzii* in gut microbiome function and the deficiency of the species in SLE patients, we investigated whether supplementation of *F. prausnitzii* restores lupus-associated microbiome dysfunction.

B6.*Sle1*.Yaa mice are a simplified congenic model of lupus that develops in males due to the Y-chromosome duplication of an X-linked locus that includes the *Tlr7* gene, combined with the *Sle1* lupus susceptibility locus^{27,28}. By integrating metagenomics, metatranscriptomics (metaT), and untargeted metabolomics, we showed that UT1 modulated the composition and active functions of the gut microbiome in the B6.*Sle1*.Yaa mice, leading to sustained carbohydrate catabolism, reprogrammed tryptophan catabolism, and augmented bile acid (BA) modifications. These microbial signatures were accompanied by reduced colonic inflammatory responses and systemic autoimmune manifestations in the host. Thus, our findings identify a probiotic candidate for alleviating lupus diseases and illuminate the potency of microbially targeted disease management. This work further emphasizes the potential of metaT- and metabolomics-guided integration for the discovery of functional microbiome signatures in autoimmune diseases.

Results

Reduced *F. prausnitzii* abundance is associated with carbohydrate metabolic deficiency in fecal metagenomes of SLE patients

Reanalysis of fecal metagenomes from a large cohort of Asian SLE patients⁶ revealed a marked depletion of butyrate-producing bacterial taxa, including multiple species of *Roseburia*, *Eubacterium*, and *Blautia*, as well as *F. prausnitzii*, whereas *R. gnavus*, *L. salivarius*, *L. gasseri*, and *E. coli* were expanded (Supplementary Fig. 1A). Notably, the abundance of *F. prausnitzii* was restored following treatment that reduced disease activity⁶ (Fig. 1A). Reanalysis of a smaller U.S. cohort of untreated SLE patients⁵ also revealed a trend toward reduced *F. prausnitzii* abundance, along with consistent depletion of several other butyrate producers, such as *Eubacterium rectale*, *Coprococcus catus*, and *Roseburia inulinivorans* (Supplementary Fig. 1B).

To examine microbial carbohydrate metabolic functions, we quantified the abundance of CAZymes and predicted their substrates in the fecal metagenomes of both cohorts. Compared to healthy controls (HCs), untreated SLE patients exhibited a distinct CAZyme profile, with stronger between-group separation observed in the larger cohort (Fig. 1B and Supplementary Fig. 1C). The CAZyme profile of treated patients shifted away from that of untreated patients, although it remained different from HCs (Fig. 1B). Glycoside hydrolase (GH) was the predominant CAZyme family affected by SLE, and most differentially enriched GHs displayed a greater magnitude of change and statistical significance in HCs than those enriched in untreated SLE patients (Fig. 1C and Supplementary Fig. 1D). Furthermore, we identified 17 CAZymes conserved between the two cohorts, 16 of which were consistently enriched in HCs, including β -1,4-galactanase GH53, β -mannanase GH113, β -glucuronidase GH79, and β -xylosidase GH30_1 (Fig. 1C and Supplementary Fig. 1D), highlighting functional conservation of microbial CAZymes despite distinct geographic origins.

A dbCAN-PUL search identified CAZyme gene clusters (CGCs), which are experimentally characterized polysaccharide utilization loci²⁹, and predicted their glycan substrates. Here, the microbiome of SLE patients showed increased abundance of CGCs targeting host-derived glycans, such as mucin, but a reduced capacity to degrade dietary fibers, including raffinose, galactan, and β -GOS (Fig. 1D and Supplementary Fig. 1E). Following treatment, the CGCs involved in the utilization of mucin, starch, and raffinose were restored to levels similar to HCs (Fig. 1D). Further analyses demonstrated that the abundance of *F. prausnitzii* was inversely correlated with the abundance of CGCs for mucins and host glycan utilization but positively correlated with the capacity of degrading starch and β -GOS (Fig. 1E). Together, these results suggest a carbohydrate catabolic deficiency in the SLE microbiome, associated with *F. prausnitzii* depletion, which is largely reversible with disease management.

Partial reversal of lupus-associated microbiome by UT1 treatment

F. prausnitzii was detected at low abundance in some lupus-prone B6.*Sle1*.Yaa and healthy control B6 mice (Supplementary Fig. 2A), and an increase in *F. prausnitzii* abundance was observed within 2 days after gavaging B6.*Sle1*.Yaa mice with strain UT1 (Supplementary Fig. 2B). Thus, we orally treated B6.*Sle1*.Yaa mice with UT1 every 2 days, starting at 3 months of age before disease development²⁸ and continuing until 5 months of age, at the time of disease manifestation. A course of 8-week treatment slightly shifted bacterial diversities, including a significant increase in Bray–Curtis distances, a measure of dissimilarity between PBS- and UT1-treated B6.*Sle1*.Yaa mice (Supplementary Fig. 2C–E). We then extended the treatment course to 12 weeks and performed longitudinal 16S rRNA analysis. Compared to PBS controls, UT1 treatment did not impact α -diversity (Supplementary Fig. 2F), but increased Bray–Curtis distances as first documented at 8 weeks (Supplementary Fig. 2G) and induced noticeable compositional changes after 12 weeks, including a

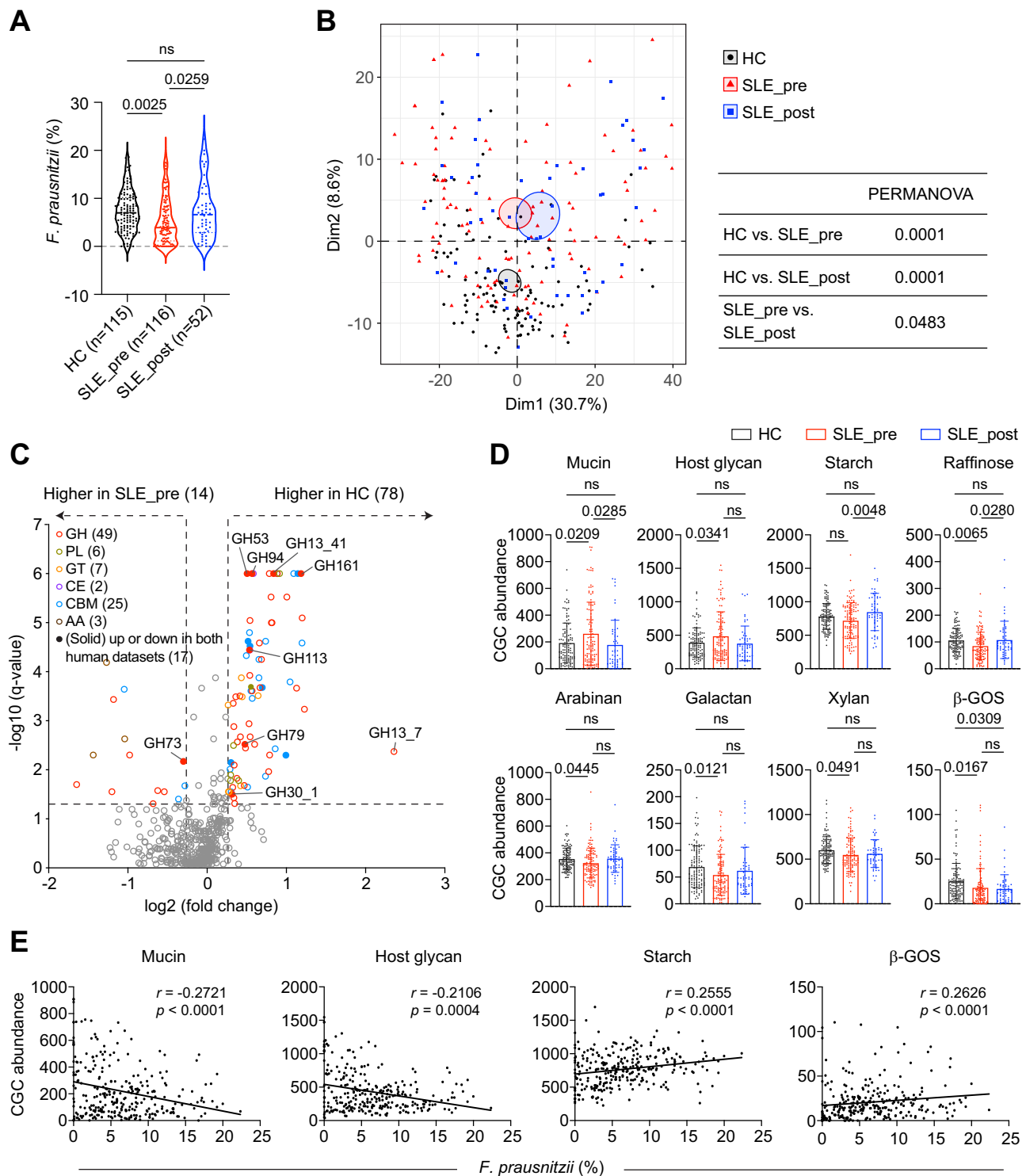


Fig. 1 | Carbohydrate metabolic profile of human SLE metagenomes. A Relative abundance of *F. prausnitzii* in the fecal metagenomes of a cohort of Asian SLE patients before and after treatment compared to healthy controls (HCs). Violin plots show the data distribution, with the median (center line) and interquartile range (25th–75th percentiles). **B** Principal component analysis (PCA) of CAZymes in the fecal metagenomes. Differences between groups were assessed by PERMANOVA. **C** Volcano plot of CAZymes differentially enriched between untreated SLE patients and HCs (fold change > 1.2; FDR-corrected $p < 0.05$, two-sided Mann–Whitney test). The number of CAZymes in each category is shown in parentheses. The CAZymes consistently affected in both Asian and U.S. cohorts are

shown as solid dots. GH glycoside hydrolase, PL polysaccharide lyase, GT glycosyltransferase, CE carbohydrate esterase, CBM carbohydrate-binding module, AA enzymes of auxiliary activities. **D** Abundance of CGCs predicted to catabolize indicated carbohydrates in the three groups of human fecal metagenomes. Data are presented as mean $\pm$ SD. **E** Spearman's correlations between the abundance of *F. prausnitzii* and CGCs responsible for degrading mucin, host glycan, starch, and β -galactooligosaccharides (β -GOS) ($n = 283$; two-sided tests). p values were calculated using one-way ANOVA plus Tukey's multiple comparisons test (**A**, **D**). ns not significant.

4

Fig. 2 | Taxonomic and functional modulation of the fecal microbiome in lupus mice by UT1 treatment. **A** Principal coordinate analysis (PCoA) of fecal metagenomes derived from B6 ($n = 3$), B6.*Sle1*.Yaa (abbreviated as *Sle1*.Yaa) ($n = 9$), or B6.*Sle1*.Yaa mice treated with UT1 for 12 weeks ($n = 6$). **B** Bray–Curtis distances between B6.*Sle1*.Yaa and B6 or UT1-treated B6.*Sle1*.Yaa and B6 metagenomes. Box-and-whisker plots show the median (center line), interquartile range (25th–75th percentiles; box), and minimum–maximum values (whiskers). p values were calculated using a two-sided Mann–Whitney test. **C** LEfSe depiction of the 17 bacterial species overlapping between B6 or UT1-treated B6.*Sle1*.Yaa mice compared to control B6.*Sle1*.Yaa mice. Species with an LDA score >2 are shown. **D** PCA of all CAZymes detected in the fecal metagenomes of B6, control B6.*Sle1*.Yaa, and UT1-

treated B6.*Sle1*.Yaa mice. **E** Volcano plot of CAZymes differentially enriched between B6 and B6.*Sle1*.Yaa mice (fold change >1.2 ; $p < 0.05$, two-tailed unpaired t -test). The number of CAZymes in each category is shown in parentheses. The CAZymes reversed by UT1 treatment are shown as solid dots. **F** Heatmap of the abundance of differentially enriched CAZymes predicted to catabolize indicated carbohydrates. The CAZymes reversed by UT1 treatment are indicated with p values in parentheses (calculated using a two-tailed unpaired t -test). **G** Correlation of CAZymes with significantly different abundance in the fecal metagenomes of both murine (Y -axis) and human (X -axis; Asian cohort) lupus compared to their respective controls. Solid dots indicate overlapping CAZymes deficient in both B6.*Sle1*.Yaa mice and SLE patients from both Asian and U.S. cohorts.

and *L. reuteri*), linked to worsened autoimmune manifestations¹¹, were the top species enriched in the lupus mice, whereas B6 mice were enriched with members of the *Muribaculaceae* family (also known as S24-7), including *Heminiphilus faecis*, *Muribaculaceae* bacterium 104_HZI, *Muribaculum intestinale*, and several uncharacterized SGBs (Supplementary Fig. 3B). Intriguingly, 17 of the 86 SGBs that differed between lupus-prone and B6 mice were restored to near B6 levels after B6.*Sle1*.Yaa mice were treated with UT1 for 12 weeks (highlighted in colors; Supplementary Fig. 3C), including the emergence of *Heminiphilus faecis* and *Muribaculum intestinale* and the depletion of *Faecalibaculum* and *Paramuribaculum* (Fig. 2C and Supplementary Fig. 3D). *Turicibacter* strain 1E2, which encodes a taurine-specific bile acid hydrolase (BSH) to process taurine-conjugated BAs³¹, was absent in most B6.*Sle1*.Yaa mice, but was detected in all UT1-treated and B6 mice (Fig. 2C and Supplementary Fig. 3D). *Bacteroides acidifaciens*, and *Parabacteroides distasonis* are documented for their capability to alleviate inflammatory responses^{32,33}; *Romboutsia ilealis*, which harbors a unique glycosyltransferase to synthesize (1,3;1,4)- β -D-glucans³⁴, responds positively to probiotic intake³⁵. The abundance of these bacteria was similar in B6.*Sle1*.Yaa and B6 mice (Supplementary Fig. 3B), but increased by UT1 gavage (Supplementary Fig. 3D).

Functional profiling of the metagenomes revealed increased abundances of multiple pathways related to glycolysis, peptidoglycan maturation, phosphatidylglycerol biosynthesis, and pyrimidine biosynthesis, and decreased pyrimidine deoxyribonucleoside salvage in B6.*Sle1*.Yaa feces compared to B6 mice, indicating enhanced potential for bacterial expansion (Supplementary Fig. 4A). Microbial degradation of purine nucleosides may reduce serum levels of urate³⁶ that could contribute to renal damage in SLE patients³⁷. UT1 notably facilitated bacterial degradation of purine nucleotides in B6.*Sle1*.Yaa mice, as indicated by several increased metagenomic pathways involved in guanosine nucleotides and purine nucleobases degradation (Supplementary Fig. 4B), suggesting that the control of purine homeostasis may be a protective microbial signature. Additionally, the *O*-antigen building block biosynthesis (*E. coli*) pathway, which generates lipopolysaccharide (LPS) substrates, was more abundant in B6.*Sle1*.Yaa mice compared to B6 controls (Supplementary Fig. 4A), whereas GDP-mannose-derived *O*-antigen building blocks biosynthesis was elevated by UT1 (Supplementary Fig. 4B). By contrast, dTDP-*N*-acetylglucosamine biosynthesis, which also produces *O*-antigen sugars for LPS assembly, was higher in both UT1-treated B6.*Sle1*.Yaa and B6 groups compared to the control B6.*Sle1*.Yaa group (Supplementary Fig. 4B). This unique pattern of *O*-glycan biosynthesis could be attributable to the differential enrichment of Gram-negative microbes (e.g., *Muribaculaceae*). UT1 treatment also restored the pathways of L-rhamnose degradation, L-tyrosine biosynthesis, and toxic formaldehyde assimilation (highlighted in red; Supplementary Fig. 4B). Together, these results suggest that UT1 partially reversed the lupus-associated microbiome, leading to the reprogramming of the microbial functional capacity.

Carbohydrate catabolic deficiency in the microbiome of lupus-prone mice

Having demonstrated an association between *F. prausnitzii* and carbohydrate metabolism in human SLE metagenomes (Fig. 1), we next profiled CAZymes in B6.*Sle1*.Yaa compared to B6 mice and examined the effect of the UT1 treatment. A principal component analysis (PCA) of 380 detected CAZyme families demonstrated a carbohydrate-utilizing profile segregating B6.*Sle1*.Yaa from B6 mice, and this separation was abrogated by UT1 (Fig. 2D). There was a total of 124 CAZymes differentially enriched between B6.*Sle1*.Yaa and B6 mice, among which 110 (88.7%) were reduced in the B6.*Sle1*.Yaa metagenomes, and 40.9% of them (45 out of 110) were restored by UT1 (Fig. 2E). Similarly, most of the annotated enzymes responsible for carbohydrate breakdown were less abundant in control B6.*Sle1*.Yaa mice compared to the B6 or UT1-treated group (Supplementary Fig. 5). The dbCAN-sub search and substrate mapping revealed a decreased abundance of CAZymes responsible for catabolizing a range of complex carbohydrates, such as arabinan, arabinogalactan, and mannans in lupus mice, most of which were significantly rescued after UT1 treatment (Fig. 2F).

Comparison of 92 differentially abundant CAZymes in the Asian SLE patients (Fig. 1C) with the 124 CAZymes differing between B6.*Sle1*.Yaa and B6 mice (Fig. 2E) identified 26 enzyme families or subfamilies that were deficient in the microbiome of both lupus mice and patients. Among them, six CAZymes, involved in the degradation of β -xylan (GH30_1), β -1,4-galactan (GH53 and CBM61), β -glucan (GH94), and α -glucan (GH13_41), were also diminished in SLE patients of the U.S. cohort (solid dots; Fig. 2G). These results suggest a role for *F. prausnitzii* in supporting a profile of microbial carbohydrate catabolism, whose deficiency may contribute to SLE development in both humans and mice.

Differential functions of the murine lupus microbiome revealed by metaT profiling

To investigate the genes and pathways actively expressed by the microbiome, metaT analysis was conducted on the fecal bacteria from B6.*Sle1*.Yaa mice treated with UT1 or PBS for 12 weeks. After removal of reads mapping to the host genome and depletion of non-coding rRNA, an average of 15.3 million mRNA reads per sample was mapped to ~1 million microbial genomes to predict the abundance of active microorganisms using MetaPhlAn4. Obtained data demonstrated a separation of the two groups of metatranscriptomes (Fig. 3A), without an impact on bacterial α -diversity (Supplementary Fig. 3A). *Muribaculaceae* and *Erysipelotrichaceae* were the major transcriptionally active bacterial families in the PBS control group, accounting for $>30\%$ of total transcribed bacteria, whereas a drastic contraction of *Erysipelotrichaceae* and a concomitant expansion of *Lachnospiraceae* were observed in the UT1-treated group (Fig. 3B). At the species level, significant metaT alterations were partly concurrent with changes in metagenomic abundance, with 17 out of 44 species consistently differing between the UT1 and PBS groups in the same direction

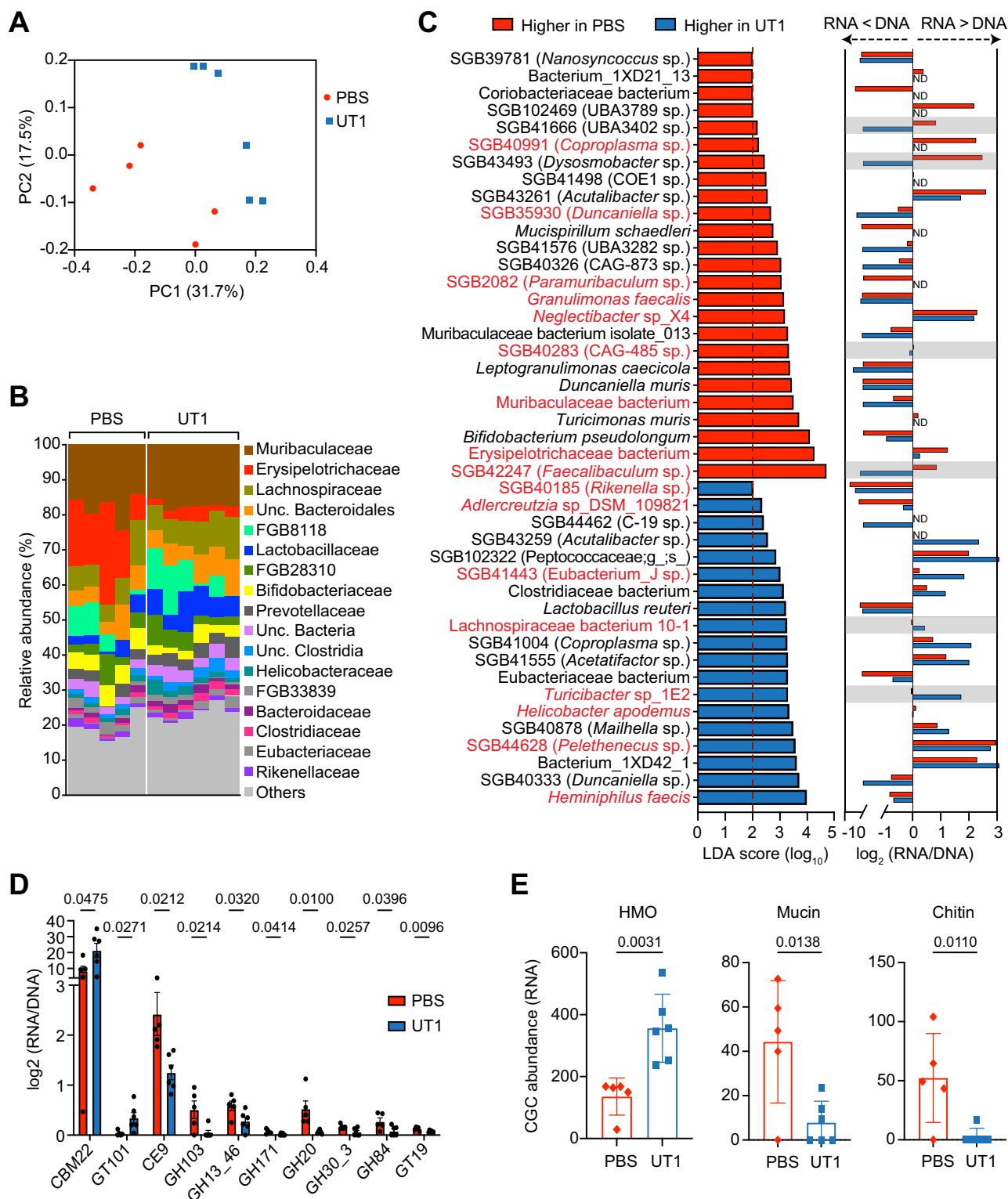


Fig. 3 | MetaT profile and active carbohydrate utilization of the fecal microbiome in lupus mice treated with UT1. **A** PCoA plot of fecal metatranscriptomes of B6.Sle1.Yaa mice gavaged with UT1 ($n = 6$) or PBS ($n = 5$) for 12 weeks.

B Distribution of transcriptionally active bacterial families in the microbiome of UT1- and PBS-treated mice. **C** LefSe analysis of differentially enriched metaT species between the UT1 and PBS groups. Species with an LDA score > 2 are shown. Species highlighted in red font also differed metagenomically in the same direction. The averaged RNA abundance of each species was normalized to their averaged

metagenomic DNA abundance in each group to evaluate bacterial activities (right panel). Species with reversed $\log_2$ (DNA/RNA) ratios between the two groups (e.g., RNA $<$ DNA in PBS versus RNA $>$ DNA in UT1) are shaded in gray. ND, RNA not detected. **D** CAZymes with RNA/DNA ratios differing between UT1 and PBS groups. **E** RNA abundance of CGCs predicted for utilizing human milk oligosaccharide (HMO), mucin, and chitin in the fecal metatranscriptomes. Bar graphs are presented as mean $\pm$ SD. p values were calculated using a two-tailed unpaired t -test (**D**, **E**).

(highlighted in red; Fig. 3C). There were 27 species for which differences were not attributed to their metagenomic abundance, and 29.6% of them (8 out of 27) were members within the order Eubacteriales (e.g., *Eubacteriaceae* bacterium and *Clostridiaceae* bacterium), indicating their transcriptional flexibility in response to intestinal environmental conditions.

To examine the bacterial transcriptomic profiles that are not solely dependent on DNA abundance, the ratios of metaT and metagenomic abundances (RNA/DNA) were calculated for each species and compared between UT1- and PBS-treated murine groups. Here, most species of *Muribaculaceae* (e.g., *Heminiphilus faecis*, *Duncaniella* sp., and *Duncaniella muris*) were over-represented by their metagenomic abundances (RNA < DNA) in both groups, whereas two species of *Lachnospiraceae* (*Acetatifactor* sp. and *Lachnospiraceae* bacterium 10-1) were over-transcribed at a greater level in the UT1 group (RNA > DNA). A complete reversal of RNA/DNA ratios was observed in six species, among which *Turicibacter* strain 1E4 was over-transcribed while *Faecalibaculum* sp. was highly suppressed due to UT1 treatment, indicating the maximal control of their activities at both transcriptional and DNA levels.

Further, among the species enriched in the PBS group, eight had undetectable RNA in the UT1 group (ND; Fig. 3C). This includes *Mucispirillum schaedleri*, a pathobiont that expands during inflammation and encodes machinery for scavenging reactive oxygen species³⁸, and *Turicimonas muris*, which may contribute to proinflammatory response³⁹. *Coriobacteriaceae* bacterium, reported to be a stress responder⁴⁰, was also not transcribed in UT1-treated mice despite the presence of DNA in all the fecal samples. In contrast, two Firmicutes species (SGB43259 and SGB44462) had no transcripts in the PBS group. It is also noted that *L. reuteri* exhibited higher abundance in the UT1 group, but its transcription was repressed (Fig. 3C).

The comparison between the transcript and DNA abundance of CAZymes demonstrated that UT1 induced the expression of xylan-targeting CBM22 and hexosyltransferase GT101, and it restricted the transcription of CAZymes implicated in peptidoglycan metabolism (CE9 and GH103), mucin degradation (GH20 and GH84), and lipid-Adisaccharide synthase (GT119), crucial for LPS biosynthesis (Fig. 3D). Additionally, compared to PBS controls, the microbiome of UT1-treated B6.Sle1.Yaa mice displayed reduced transcription of CGCs utilizing mucin and chitin and increased expression of the CGC responsible for catabolizing human milk oligosaccharide (HMO) (Fig. 3E), most likely a murine counterpart.

Further examination of the two metatranscriptomes demonstrated that the vast majority of differentially expressed genes ($p < 0.001$ and normalized RNA reads > 10) had higher RNA abundance in the PBS group compared to UT1-gavaged group (Fig. 4A). To identify transcriptional changes that were induced unequally under the two host conditions, the log₂-transformed RNA/DNA ratios of these genes were further compared between UT1 and PBS groups. Thus, genes with a comparable RNA/DNA ratio were similarly transcribed between the two groups, and their RNA alterations were attributable to differential DNA abundances, whereas the genes with a significantly different RNA/DNA ratio (indicated by p values; Fig. 4A) responded differently to environmental clues. Here, we found that genes highly sensitive to oxidative stress, including rubrerythrin, rubredoxin, and peroxiredoxin, were induced in both groups [$\log_2$ (RNA/DNA) > 0], but the magnitude of the induction was significantly dampened by UT1 treatment (Fig. 4A), suggesting a controlled oxidative status in the gut. Additionally, a set of protein-coding rRNA genes (e.g., ribosomal proteins S13, S15, S31, and L33) and the elongation factor P were over-transcribed in PBS mice, whereas these genes were rarely expressed in the UT1 group [$\log_2$ (RNA/DNA) < 0] (Fig. 4A). Moreover, the metatranscriptome of the UT1 group was enriched with several pathways for purine nucleotide degradation and depleted for adenosine and guanosine nucleotide biosynthesis pathways (Fig. 4B). This suggests a

restriction of bacterial translation and replication potentially leads to the control of dysbiotic bacterial expansion. Interestingly, the chitin derivatives degradation pathway was quiescent in UT1-treated mice, despite its significantly higher DNA abundance (Fig. 4B).

Several RNA pathways were also disproportionate to their metagenomic contributions, including those related to carbohydrate metabolism (e.g., stachyose and galactose degradation), glycolysis (e.g., pyruvate fermentation to acetate and lactate), and oxidative stress (e.g., heme B biosynthesis). In addition, 8 out of 28 significant metaT pathways were also metagenomically different, including increased L-serine and glycine biosynthesis and NAD salvage, and decreased L-histidine biosynthesis and toxic formaldehyde assimilation in the UT1 group (Fig. 4B). Overall, these results illustrate the potency of UT1-dependent transcriptional regulation of microbiome functions.

Microbiota-associated metabolic programming by UT1

To further interrogate the functional changes of the gut microbiome, we conducted an untargeted metabolomics analysis on the fecal samples collected from the same UT1- and PBS-treated B6.Sle1.Yaa mice used for the metaT profiling. High-resolution liquid chromatography-mass spectrometry (LC-MS) analyses showed that UT1 notably shifted the fecal metabolome of the lupus mice, identified by both positive and negative ionizations (Fig. 5A). Tryptophan metabolism, glyoxylate and dicarboxylate metabolism, and pentose phosphate pathway (PPP) were differentially enriched between the fecal samples of UT1- and PBS-treated mice (Fig. 5B). By comparing to a library of standards, 51 metabolites were identified with intensities significantly differing between the two groups (Fig. 5C). Metabolites with potent antioxidant potential, particularly ascorbate, ferulate, and dihydrocaffeic acid, were found at significantly higher levels in UT1 group compared to PBS control (Fig. 5C). Several metabolites positively correlated with their biosynthetic metaT pathways. Elevated serine and aspartate biosynthesis (Fig. 4B) corresponded to increased levels of these amino acids in the fecal samples of UT1-treated mice, whilst reduced lysine biosynthesis was associated with an enrichment of several lysine catabolites, including 5-aminopentanoate, glutarate, and 2-hydroxyglutarate (Fig. 5C). Enhanced transcription of NAD salvage pathway II (Fig. 4B) could lead to increased levels of nicotinamide (Fig. 5C), a precursor for NADPH.

Further, we detected higher amounts of pentose sugars (arabinose, arabitol, and xylose) in the UT1 group, consistent with the prediction of increased abundance of CAZymes that release these sugars from complex carbohydrates (e.g., arabinogalactan and xylan) (Fig. 2F). The level of gluconate, which enters oxidative PPP generating reducing equivalent NADPH⁴¹, and the transcript of ribulokinase that phosphorylates pentose for PPP (Fig. 5D) were correspondingly elevated. Additionally, the conversion of glycolate into serine through glyoxylate and dicarboxylate metabolism (Fig. 5B, C) also robustly produces NADPH to maintain cellular antioxidant systems⁴². These metabolic pathways were all activated by UT1, indicating active control of cellular oxidative stress, in accordance with the reduced expression of stress-inducible genes in the fecal metatranscriptomes (Fig. 4A).

Bacterial catabolism of tryptophan generates indoleacetic acid through the oxidative pathway, and indoleacrylic acid through the reductive pathway (Fig. 5E)^{43,44}, both of which are aryl hydrocarbon receptor (AhR) ligands that regulate the immune response and inflammation^{45,46}. These metabolites, along with the expression of their catalytic enzymes (e.g., *iorB*) (Fig. 5C, E, F), were enriched in the microbiota of UT1-treated mice, wherein the expression of *kfa* and the intensity of formylkynurenine in the kynurenine pathway tended to be repressed. Formyl-5-hydroxykynurenine is a catabolite of serotonin primarily produced by intestinal enterochromaffin cells. 5-Hydroxy-N-formylkynurenine is derived from 5-hydroxy-L-tryptophan, the only precursor for serotonin. The reduced level of both metabolites

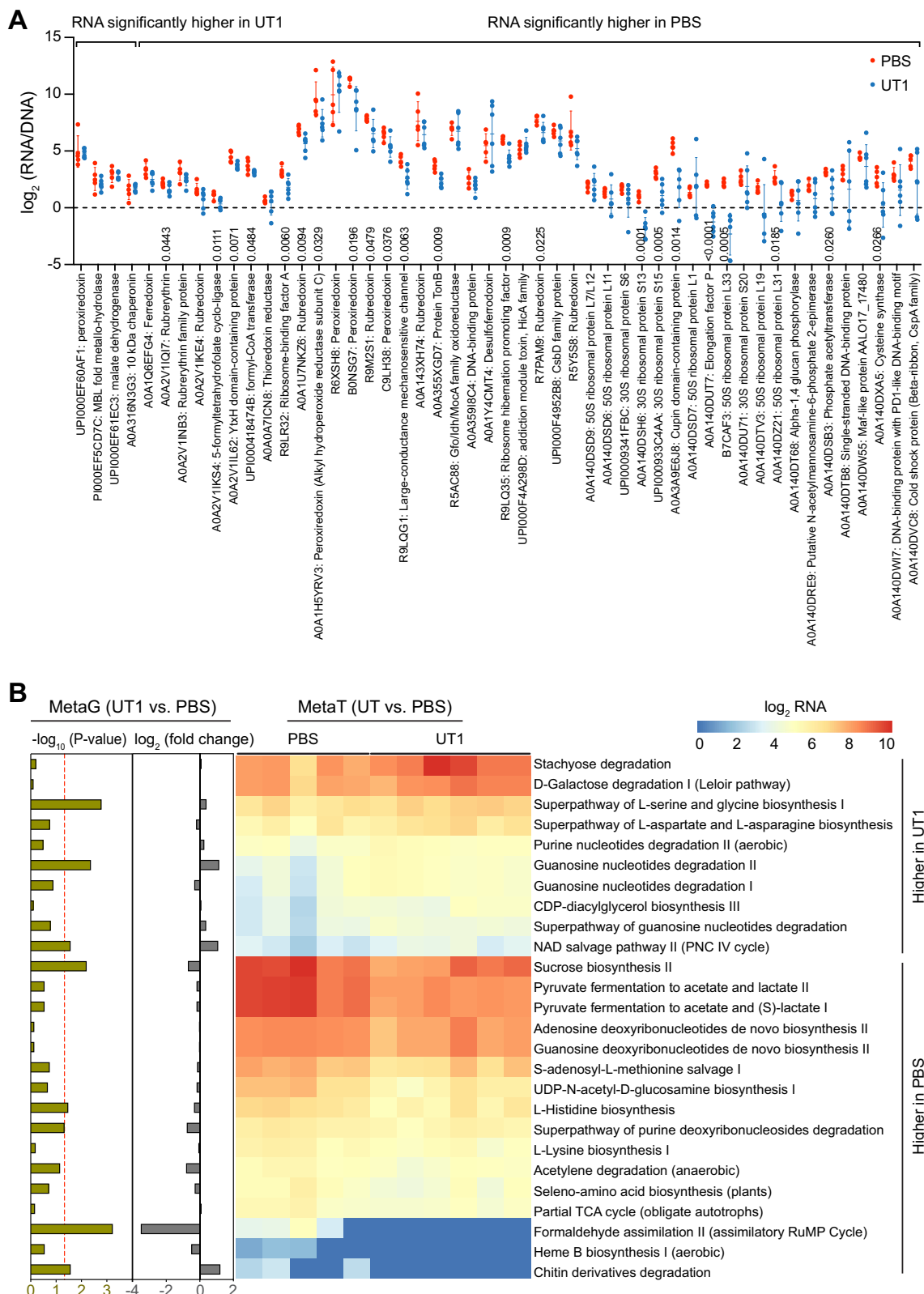
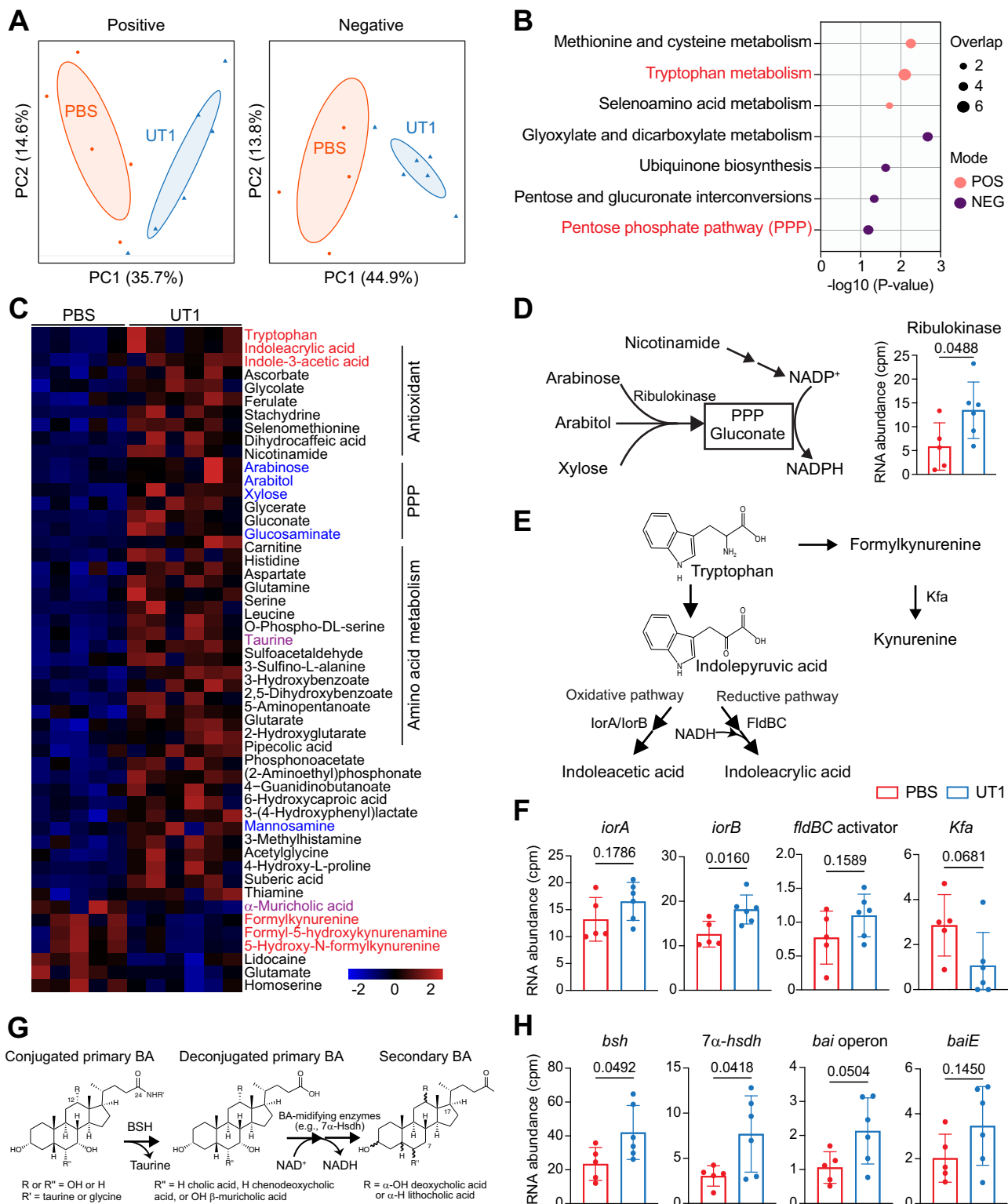


Fig. 4 | Transcriptional landscape of the fecal microbiome. A Log₂-transformed RNA/DNA ratios of bacterial gene families in the fecal microbiome of UT1- ($n = 6$) and PBS-treated ($n = 5$) B6.Sle1.Yaa mice. Only genes with RNA abundance significantly differing between UT1 and PBS groups (normalized RNA abundance > 10 ; $p < 0.001$, two-tailed unpaired t -test) are plotted. Each dot represents the RNA/DNA ratio obtained from a single mouse. Genes with $\log_2$ (RNA/DNA) > 0 (above the dashed line) were over-transcribed (RNA $>$ DNA). Genes with significantly different

RNA/DNA ratios between the UT1 and PBS groups are also indicated with p values (two-tailed unpaired t -test). Data are presented as mean $\pm$ SD. **B** Heat map of differential metaT pathways (right panel) ranked by pathway abundance (highest on the top), in comparison to their metagenomic (metaG) contributions in the same UT1- and PBS-gavaged mice (left panel). The red dashed line indicates the p -value of 0.05 (two-tailed unpaired t -test).



(Fig. 5C) is likely a reflection of controlled tryptophan metabolism in host cells.

Finally, host-derived primary BAs, predominantly taurine-conjugated BAs, are deconjugated by bacterial bile salt hydrolase (BSH) in the gut, releasing taurine and regenerating deconjugated BAs, which are dehydroxylated by microbial BA-modifying enzymes, particularly 7 α -hydroxysteroid dehydrogenase (7 α -Hsdh), to form bioactive secondary BAs (Fig. 5G)⁴⁷. Compared to PBS controls, the feces of UT1-treated mice had reduced levels

of α -muricholic acid, a murine-specific primary BA, and increased taurine, taurine-associated 3-sulfinyl-L-alanine, and sulfoacetaldehyde levels (Fig. 5C). Correlatively, a higher expression of *bsh*, 7 α -*hsdh*, and the *bai* operon (Fig. 5H), responsible for bacterial BA dehydroxylation⁴⁷, was detected, suggesting enhanced BA-modifying activities in the gut. Together, these results suggest that UT1 transcriptionally and metabolically reprograms the microbiome to potentially resist disease progression in B6.Sle1.Yaa mice.

Fig. 5 | Functional modulation of fecal metabolomes by UT1. **A** PCA plot of metabolite features identified by positive and negative ionizations in the feces of B6.*Sle1*.Yaa mice gavaged with UT1 ($n = 6$) or PBS ($n = 5$) for 12 weeks. **B** Metabolic pathways with significantly differing intensities in positive (POS) and negative (NEG) ionizations (empirical $p < 0.05$, estimated using permutation test). The overlapped size indicates the number of significant metabolic features mapped to corresponding pathways. **C** Heatmap showing differentially enriched metabolites between UT1 and PBS groups. Carbohydrates (blue) and metabolites involved in tryptophan metabolism (red) and BA metabolism (purple) are highlighted. **D** Metabolites and the *Ribulokinase* gene in the PPP. The pentose metabolites (arabinose, arabitol, and xylose) produced by the breakdown of complex

carbohydrates through CAZymes can be converted by ribulokinase into PPP substrates, generating reducing equivalent NADPH. **E, F** Tryptophan catabolism generates either the oxidative pathway product indoleacetic acid, catalyzed by IorA/B (indolepyruvate oxidoreductase subunit A/B), or the reductive pathway product indoleacrylic acid, catalyzed by FldBC (phenyllactate dehydratase subunit B/C), in the fecal microbiome of UT1-treated mice. Formylkynurenine and Kfa (kynurenine formamidase) produce kynurenine. Bar graphs depict the expression levels of the genes within this pathway in the PBS and UT1 metatranscriptomes. **G, H** BA metabolism and expression of the corresponding BA-modifying genes. All bar graphs are presented as mean $\pm$ SD. p values were calculated using a two-tailed unpaired t -test (**D, F**, and **H**).

Regulation of colonic immune responses via UT1 treatment

Knowing that gut microbiota and associated metabolism crucially influence the host mucosal immune responses⁴⁸, including in lupus^{3,49}, we immunophenotyped the colon of B6 controls and B6.*Sle1*.Yaa mice treated with UT1 or PBS. 8-week treatment with UT1 reduced the number of colonic TNF α ⁺ dendritic cells (DCs), with a trend toward decreased Th17 cells (Supplementary Fig. 6A). After 12 weeks of treatment, the expansion of colonic DCs, including TNF α ⁺ DCs, in B6.*Sle1*.Yaa mice was completely normalized by UT1 to non-autoimmune levels (Fig. 6A). Notably, the frequency of total FoxP3⁺ Treg, IL-10⁺ FoxP3⁺ Treg, and ROR γ ⁺ FoxP3⁺ Treg cells was reduced in the colon of lupus mice versus B6 controls, whereas UT1 treatment increased the frequency of these populations (Fig. 6B and Supplementary Fig. 6B). In addition, the frequency and number of Th17 cells, including IL17A⁺ and ROR γ ⁺ FoxP3⁺ populations, were elevated by the autoimmune condition and decreased by UT1, albeit to the level still significantly higher than B6 controls (Fig. 6C and Supplementary Fig. 6B). Accordingly, the diminished Treg/Th17 cell ratio in B6.*Sle1*.Yaa mice were partially restored by UT1 (Fig. 6D), and the expression of pro-inflammatory cytokines, including *Ifng*, *Tnfa*, *Il1b*, and *Il6*, correspondingly declined in colonic tissues (Fig. 6E).

Correlation analyses between immune populations and fecal metabolites in the same animals revealed seven metabolites that were positively associated with the number of colonic Treg cells (Fig. 6F). These metabolites were all enriched in UT1 group, and some of them have been reported to induce Treg cell differentiation, including indoleacetic acid that activates *FoxP3* transcription and attenuates inflammation^{50,51}, as well as carnitine and 2-hydroxyglutarate, both of which may skew T cell metabolism toward oxidative phosphorylation, increasing Treg cell frequency and reducing Th17 polarization^{52,53}. The anti-inflammatory metabolites ferulate⁵⁴, mannoseamine (related to antioxidant PPP), phosphonoacetate (PAA) and pipercolic acid, whose gut deficiency are implicated in dysbiosis^{55,56}, were positively associated with Treg numbers (Fig. 6F). PAA also showed a positive correlation with the frequency of Tregs and a stronger negative correlation with the frequency of Th17 cells (Supplementary Fig. 6C). Supplementation of PAA in the drinking water of B6.*Sle1*.Yaa mice slightly reduced the frequency of colonic ROR γ ⁺ FoxP3⁺ and IL-17⁺ Th17 cells (Supplementary Fig. 6D). Thus, these results highlight the role of UT1-programmed microbial metabolism in modulating colonic immune response during disease progression.

Inhibition of systemic autoimmune responses by UT1

Next, we examined the lupus-associated autoimmune phenotype in the spleen of B6.*Sle1*.Yaa mice treated with UT1 or PBS for 12 weeks, in parallel with PBS-treated B6 controls. Here, UT1 treatment reduced the spleen weight and total splenocyte numbers (Fig. 7A) and restricted the lupus-induced expansion of neutrophils and monocytes (Fig. 7B, C). UT1 also normalized the number of total CD4⁺ T cells, including FoxP3⁺ Tregs, IL-10⁺ FoxP3⁺ Tregs, IFN γ ⁺ IL-17A⁺ Th17 cells, and IFN γ ⁺ IL-17A⁺ Th1 cells (Fig. 7D). Additionally, the lupus Tfh cells and the Tfr/Tfh ratio were also significantly restored toward B6 controls by UT1

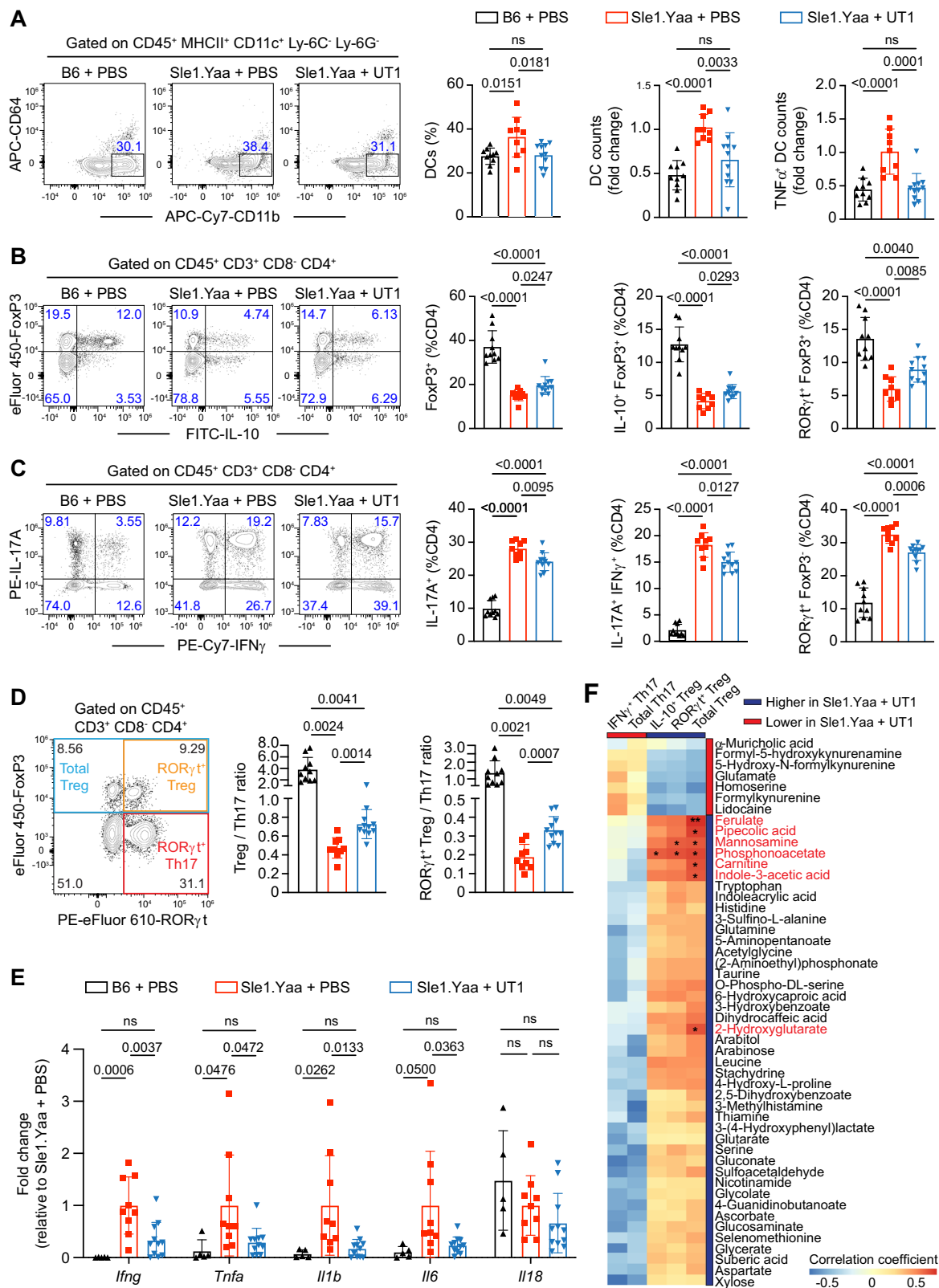
(Fig. 7E). Although Treg and Tfr cells were increased in lupus mice compared to B6 controls, these cells had reduced expression of FoxP3, which was partially rescued by UT1 (Fig. 7D, E), suggesting a restoration of immune tolerance. Consistently, the number of germinal center (GC) B cells and atypical B cells (ABCs), which play a critical role in the production of lupus autoantibodies, was modestly but significantly reduced in UT1-treated B6.*Sle1*.Yaa mice (Fig. 7F). Furthermore, the expression of *Il10*, *Ifng*, *Ccl3*, and a panel of IFN-I-stimulated genes, including *Isg15*, *Ifit1*, *Ifit3*, *Ifnar2*, *Rsad2*, and *Oasl2*, was reduced in total splenocytes of UT1-treated lupus mice, with most transcripts being statistically indistinguishable from non-autoimmune controls (Fig. 7G). There was also a significant reduction of serum anti-dsDNA IgG and anti-dsDNA IgG2c in the UT1 group (Fig. 7H). In contrast to the overall reductions in cell numbers, UT1 treatment only significantly modified the frequency of monocytes, effector CD4⁺ T (Teff) cells, naïve T (Tn) cells, and GC B cells (Supplementary Fig. 7A–E). Together, these results support a crucial role for UT1 in systemically suppressing autoimmune pathogenesis.

Reduced renal pathology in UT1-treated lupus-prone mice

Finally, we evaluated the effect of UT1 on the kidney, the main target organ in murine models of lupus. Analysis of PAS-stained sections showed that UT1 treatment reduced the glomerular size without impacting the glomerular number in B6.*Sle1*.Yaa mice (Fig. 8A, B). Renal pathology scores were also reduced in UT1-treated mice compared to PBS-treated controls (Fig. 8C). Lupus nephritis is initiated by the deposition of immune complexes formed by autoantibodies and complement C3⁵⁷. As a measure of autoantibody deposition, we assessed the deposition of IgG2c, the most pro-inflammatory IgG isotype. UT1 treatment reduced the size but not the number of IgG2c-positive glomeruli, as well as the corresponding amount of bound IgG2c. Similar reductions were obtained for C3-positive glomeruli (Fig. 8D–F). Taken together, these results suggest the UT1-treatment ameliorates autoimmune-induced pathology in the host.

Discussion

The development of SLE involves many genetic and environmental factors, and clinical standard of care mostly relies on nonspecific immunosuppressive drugs^{58,59}. Probiotics, generally considered safe, have been proven to be effective in the treatment and alleviation of inflammatory disorders^{60,61}. Several studies conducted in pre-clinical models of lupus, as well as in SLE patients, have globally suggested a beneficial effect of probiotics, mainly *Lactobacillus* and *Bifidobacterium*, on various clinical manifestations or disease biomarkers of lupus⁶². However, mechanistic insights are lacking, including the effect of the probiotics on the microbiome and the mucosal environment. Given the critical role of gut dysbiosis in inciting and exacerbating SLE⁵⁹ and that a deficiency of *F. prausnitzii* has been documented in human SLE patients⁶, we rationalized that oral supplementation of *F. prausnitzii* may confer protection against disease progression. Thus, we comprehensively profiled the impact of *F. prausnitzii* on the gut microbiome and demonstrated that the persistent UT1 treatment,



started at an early stage prior to disease manifestation, mitigated intestinal and systemic inflammatory responses and reduced renal pathology in a lupus-prone mouse model, which was associated with a profound remodeling of the composition and activity of the dysbiotic lupus microbiome.

Numerous human and rodent model studies have been conducted to elucidate the association between SLE and gut

microbiome^{4-6,49,63,64}. While it is recognized that gut dysbiosis is an integral promoter of SLE pathogenesis, variable and even discrepant results in bacterial taxa across different cohorts of SLE patients and mouse models have been reported^{63,65}, rendering the functional significance of these changes ambiguous. This necessitates a deeper understanding and interrogation of the gut microbiome using approaches that link bacterial abundances with their transcriptional

Fig. 6 | Increased colonic Treg and reduced Th17 cell responses by UT1.

A Representative flow cytometric plot, frequency, and relative abundance of colonic DCs and TNF α ⁺ DCs in B6.Sle1.Yaa mice treated with UT1 ($n = 11$) or PBS ($n = 9$) for 12 weeks, and PBS-treated B6 controls ($n = 10$). Cell frequency indicates the percentage of DCs within the parent population. Fold changes in cell numbers are shown relative to the mean value in PBS-treated B6.Sle1.Yaa mice.

B, C Representative flow cytometric plots and frequencies of Treg and Th17 cell subsets in the 3 groups of mice after 12 weeks of treatment. **D** Representative flow cytometric plot and ratios of Treg/Th17 and ROR γ ⁺ Treg/Th17 cells. **E** Relative expression of pro-inflammatory cytokines in distal colonic tissues of B6.Sle1.Yaa

mice treated with UT1 ($n = 11$) or PBS ($n = 9$) for 12 weeks, in comparison to PBS-treated B6 controls ($n = 5$). **F** Correlations between immune populations and differentially enriched metabolites obtained from the same cohorts of mice ($n = 5$ for PBS and $n = 6$ for UT1). Significant metabolite-immune correlations, determined by Spearman's correlation coefficients, are highlighted in red font based on the criteria ($|r| > 0.75$ and $FDR < 0.05$). * $FDR < 0.05$ and ** $FDR < 0.01$. All bar graphs are presented as mean $\pm$ SD. p values were calculated using Welch ANOVA with Dunnett's T3 multiple comparisons test (**A–D**) or ordinary one-way ANOVA with Tukey's multiple comparisons test (**E**).

and metabolic activities, thus allowing for the dissection of community phenotypes that are not only compositionally, but more importantly, functionally associated with disease conditions. To examine the functional changes of the lupus microbiome, we and others have assessed for correlations between metagenomics and metabolomics data^{4,66–68}, whereas no metaT analysis has been reported so far on SLE. The absence of correlative studies between microbial transcriptional pathways, and the corresponding synthesized or degraded metabolites, hinders the understanding of the contributions of microbial metabolic functions to disease outcomes. Indeed, the fecal metabolome can be readily confounded by host-derived compounds, and various microbial pathways may be linked to the same metabolites. The unique combination of integrated metagenomics, metaT, and metabolomics, employed in this study, provided faithful functional signatures of the lupus microbiome, which were modulated by a single commensal microorganism to alleviate the lupus disease.

Metagenomics profiling unraveled that UT1 remodeled the composition of the B6.Sle1.Yaa microbiome toward that of B6 controls. The abundance of 17 species was significantly restored to the non-autoimmune level, including the deficiency of *Turicibacter* strain 1E2, which is crucial for host BA metabolism^{31,69}, and the expansion of *Faecalibaculum*, which has been reported to induce epithelial IFN γ response through the crosstalk involving epithelial cells and eosinophils³⁰. As observed in B6 mice after UT1 treatment for 2 weeks²⁵, increased abundance of *Turicibacter* and diminished levels of *Lachnospiraceae* 14-2 (SGB41446) and *Neglectibacter* sp.X4 were also detected in the lupus-prone mice after UT1 gavage, suggesting the existence of UT1-dependent microbiome changes independent of disease status. UT1 increased the abundance of *L. johnsonii* in the fecal metagenomes of B6 mice²⁵. Here, the transcription level of *L. reuteri* was elevated in UT1-treated lupus mice compared to PBS-treated controls; however, it was restricted when compared to its DNA abundance (RNA < DNA).

Several studies have shown that oral administration of *Lactobacillus* species, including *L. johnsonii* and *L. reuteri*, reduced inflammation and may delay disease progression in lupus-prone mice^{62,70,71}. However, it has also been reported that *L. reuteri*, but not *L. johnsonii*, induces IFN-I responses and drives autoimmune manifestations in a TLR7-dependent mouse model of SLE¹¹. Here, the metagenomic abundance of *L. johnsonii*, *L. reuteri*, and *L. intestinalis* was all higher in B6.Sle1.Yaa mice than that in B6 mice, and increased abundance of *L. gasseri* and *L. salivarius* was also observed in a cohort of lupus patients. Given the repressed transcription of *L. reuteri* in the fecal metatranscriptomes, its functional contribution to disease progression, particularly in the UT1-conditioned microbiome, may require further mechanistic investigations. Additionally, *E. gallinarum* and *R. gnavus* have also been reported to exacerbate the lupus disease in several mouse models^{8,9,72} and human SLE patients^{8,12,13}. *E. gallinarum* was detected in the metagenomes of some B6.Sle1.Yaa mice (6 out of 15) at low abundance (0.0038% on average in positive mice), but it was absent in the metatranscriptomes, whereas *R. gnavus* was undetectable in both analyses, ruling out their possible disease contributions in the B6.Sle1.Yaa mice. These observations highlight the importance of examining the transcriptional activity as an integrative functional

output of the microbiome. Indeed, paired metagenomic and metaT analyses demonstrated that the abundance of mRNA species was not necessarily similarly represented by their DNA contributions but was greatly influenced by intestinal environmental conditions. Several members of Clostridia (e.g., *Acetatifactor*), which are highly sensitive to oxygen, were over-transcribed in the UT1 group, whereas *Muribaculaceae* that show moderate oxygen tolerance were over-represented (RNA < DNA) in both groups⁷³, potentially indicating a controlled oxygen status in the gut of UT1-gavaged mice. Consistently, oxidative stress-sensing genes, including peroxiredoxins and rubredoxins, were transcribed at a lesser magnitude in the metatranscriptomes of the UT1-treated mice compared to PBS-treated controls.

Overactivated glycolysis in T and B cells plays a crucial role in SLE pathogenesis and autoantibody production, and enzymatic inhibition of glycolysis via 2-deoxy-D-glucose (2DG) reverses autoimmune phenotype^{74,75}. Interestingly, transfer of fecal microbiota derived from 2DG-treated mice to antibiotics pre-treated lupus-prone mice prevents the development of the disease⁶⁸. Here, we showed by metagenomics profiling, that lupus-prone mice also displayed enhanced glycolytic potential within their microbiome as compared to B6 controls, raising the possibility that aberrant microbial glycolysis may also be a biomarker of lupus that may be targeted by glycolysis inhibitors to alleviate dysbiosis. The microbiome of the lupus mice was also highly enriched with pathways involved in protein translation and nucleotide biosynthesis, which are required for dysbiotic bacterial expansion. The repression of such pathways or the degradation of their substrates (e.g., purine nucleotides) by UT1 was correlated with significantly improved disease outcomes.

We presented here the first demonstration that a carbohydrate catabolic deficiency in the gut microbiome of the lupus-prone mice and human SLE patients, leads to impaired genetic capacity to utilize a range of complex carbohydrates. Instead, both human and murine lupus microbiome had increased abundances of CAZyme clusters for degrading mucins, which may contribute to intestinal barrier dysfunction, potentially leading to bacterial extraintestinal translocation, as previously reported^{8,9,11}. Despite the considerable differences between human and mouse microbiome, several conserved CAZymes have been identified, and more intriguingly, the abundance of *F. prausnitzii* correlated positively with the carbohydrate-degrading capability of the human microbiome. We previously showed that UT1 supports the carbohydrate catabolism of the microbiome in B6 mice and in vitro culture of UT1-conditioned fecal microbiota in the presence of the complex carbohydrate facilitates the anaerobic bacterial growth and metabolite production²⁵. Here, we further demonstrated that the treatment of lupus-prone mice with UT1 significantly rescued the carbohydrate metabolic deficiency, once again highlighting the crucial role of *F. prausnitzii* in supporting carbohydrate catabolism in both mice and humans to potentially resist the development of inflammation. Accordingly, carbohydrate fermentation of arabinan and xylan produced pentose, including arabinose, arabitol, and xylose, which metabolically supported the bacterial PPP to generate NADPH that directly combats oxidative stress⁷⁶. Additionally, metabolites with potent antioxidant potential (e.g., ascorbate and ferulate) were also enriched, and the stress-inducible transcripts were

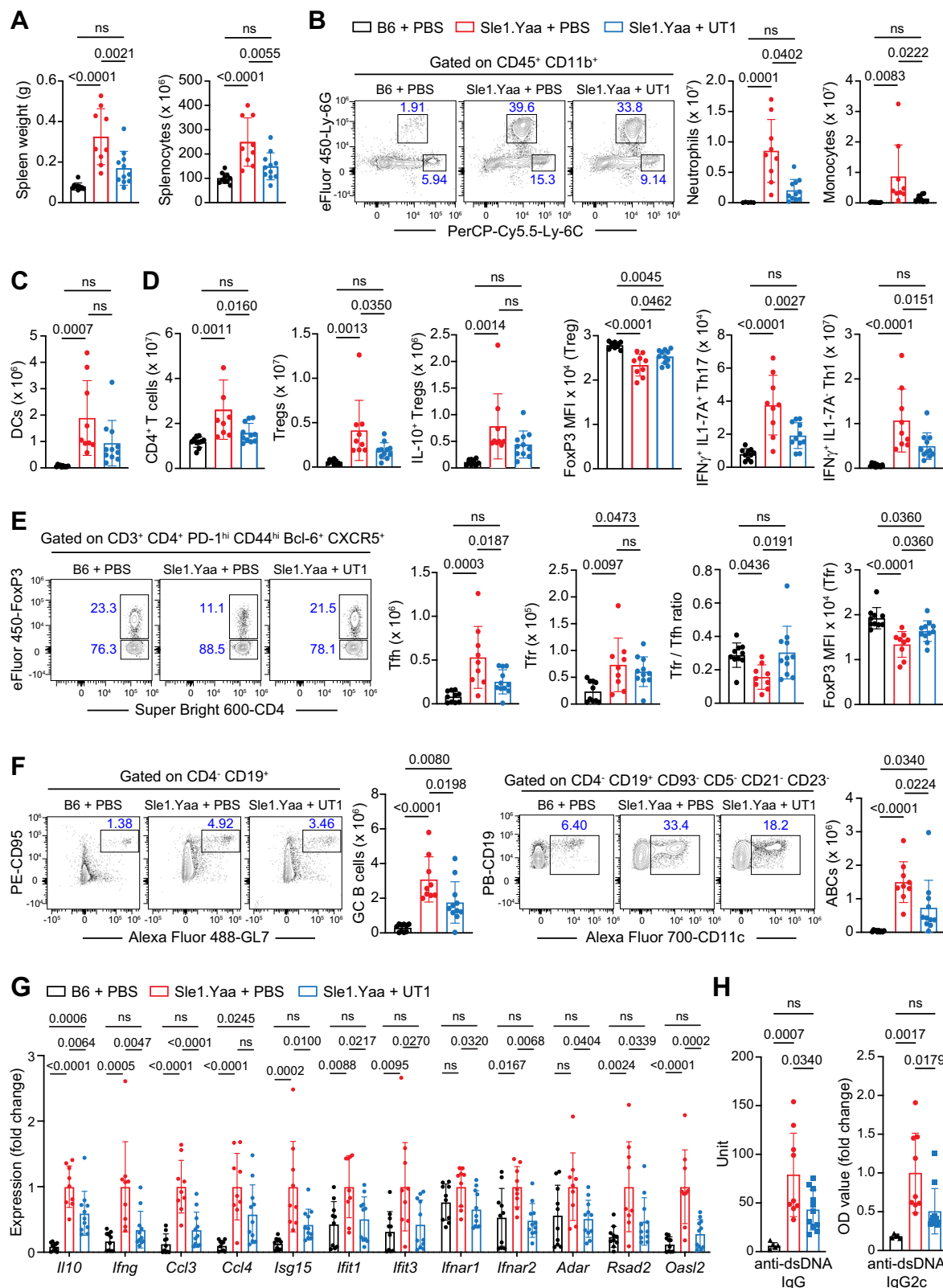


Fig. 7 | Inhibition of systemic autoimmune activation by UT1. **A** Spleen weight and total splenocytes in B6 mice treated with PBS, and B6.Sle1.Yaa mice treated with UT1 or PBS for 12 weeks. **B** Representative flow cytometric plots and numbers of splenic neutrophils and monocytes. **C, D** Numbers of splenic DCs and $CD4^+$ T cell subsets, including Treg, Th17, and Th1 cells, as well as mean fluorescence intensity (MFI) of FoxP3 in Treg cells. **E** Representative flow cytometric plots and numbers of splenic Tfh and Tfr cells, as well as FoxP3 MFI in Tfr cells. **F** Representative flow cytometric plots and numbers of splenic germinal center B (GC B) cells and ABCs in

lupus mice treated with UT1 versus controls. **G** RT-qPCR quantification of lupus-associated cytokines (*Il10* and *Ifng*), chemokines (*Ccl3* and *Ccl4*), and IFN- γ -stimulated genes in total splenocytes of the indicated treatment groups. **H** Serum anti-dsDNA IgG and IgG2c. Data are pooled from two independent experiments (B6 + PBS, $n = 10$, except $n = 5$ for neutrophils and autoantibody assays; Sle1.Yaa + PBS, $n = 9$; Sle1.Yaa + UT1, $n = 11$). Data are presented as mean $\pm$ SD. p values were calculated using ordinary one-way ANOVA with Tukey's multiple comparisons test (**A–H**). ns non-significant.

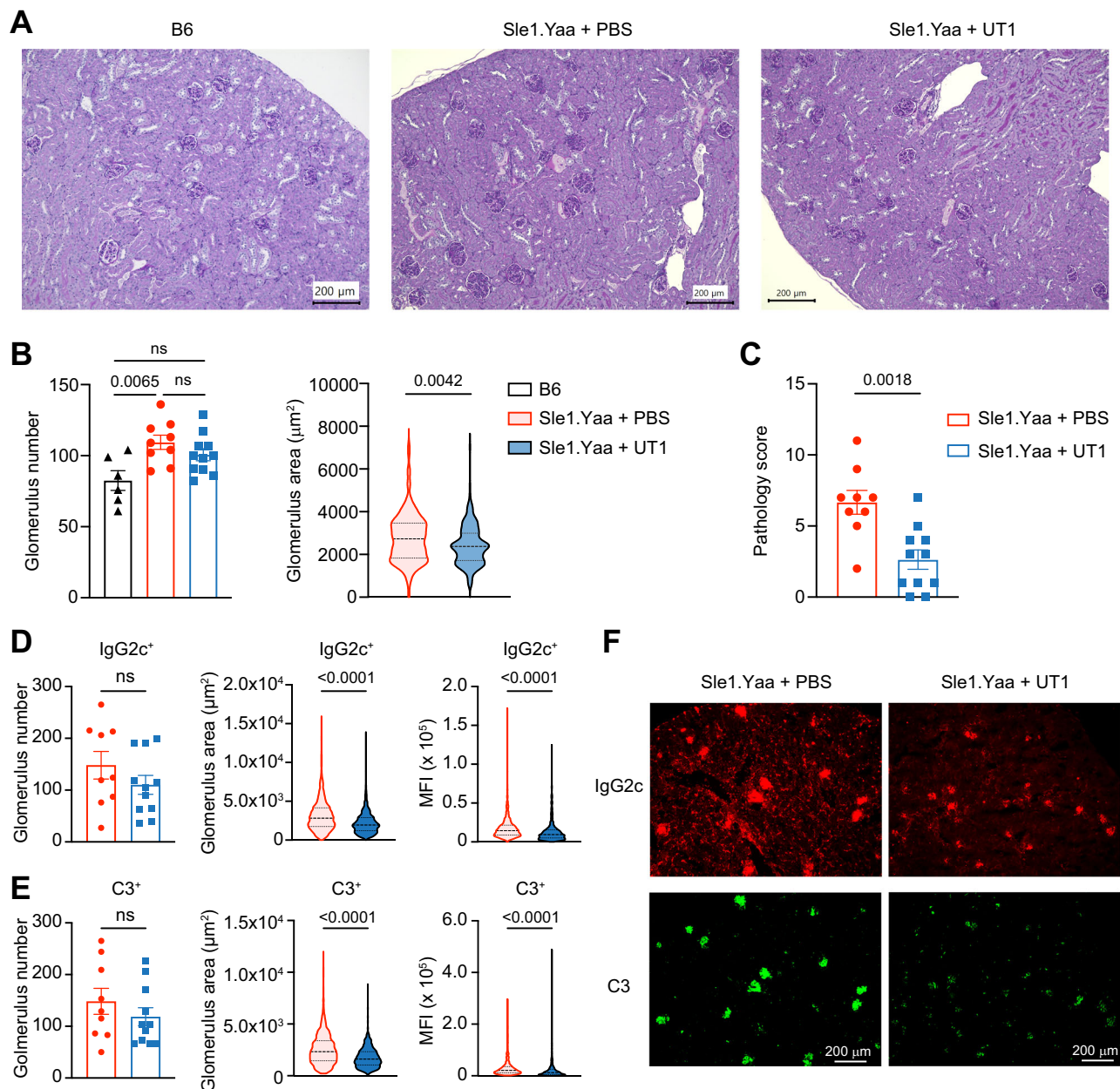


Fig. 8 | Mitigation of lupus nephritis in lupus-prone mice treated with UT1. **A** Representative PAS-stained kidney section. **B** Glomerulus numbers and individual surface area in kidney sections of B6 and Sle1.Yaa mice treated with UT1 or PBS for 12 weeks. **C** Renal pathology score. **D, E** Numbers and individual surface area of IgG2c⁺ or C3⁺ glomeruli with corresponding MFI. **F** Representative IgG2c and C3 staining in each group. Data are pooled from two independent experiments

(B6, $n = 6$; Sle1.Yaa + PBS, $n = 9$; Sle1.Yaa + UT1, $n = 11$). Bar graphs are presented as mean $\pm$ SD. Violin plots show the data distribution, with the median (center line) and interquartile range (25th–75th percentiles). p values were calculated using ordinary one-way ANOVA plus Tukey's multiple comparisons test (**B**, left panel) or two-sided Mann–Whitney test (**B**, right panel; **C–E**). ns non-significant.

correspondingly reduced in the UT1-gavaged mice. This active control may be important for preventing oxidative stress-induced Treg apoptosis and impairment in suppressive function^{77,78}.

Gut microbial catabolism of tryptophan can be directed by carbohydrate substrates toward indole, associated with inflammation, or toward protective indoleacetic acid and indoleacrylic acid⁴⁴. Mono-saccharides such as arabinose and xylose are known to repress the indole-producing pathway in *E. coli*^{79,80}, and addition of these sugars into the fecal cultures shifted the indole pathway toward protective derivatives⁴⁴. Accordingly, arabinose and xylose, enriched in the fecal microbiome of UT1-treated mice, were associated with a rewired tryptophan catabolism toward indoleacetic acid and indoleacrylic

acid, which may directly support the maintenance and function of Tregs and control inflammatory responses^{45,50,51}.

Microbially modified secondary BAs have been reported to directly bind to ROR γ t, leading to the generation of ROR γ t⁺ FoxP3⁺ Tregs and suppression of Th17 cell responses^{81,82}. Increased levels of primary BAs, including taurocholic acid, and a trend of decreased secondary BAs were also observed in patients with SLE^{83,84}. Here, UT1 treatment reduced the level of α -muricholic acid and enhanced the transcription of BA-modifying enzymes (e.g., *bsh* and *7 α -hsdh*), associated with increased frequencies and numbers of Treg cells and reduced Th17 cell responses in the colon.

A few studies have reported that PAA inhibits viral DNA replication^{85–87}, but none have investigated a potential immunological function. Through metabolite-immune population integration, we identified a negative correlation between fecal PAA levels and colonic Th17 cells. Interestingly, supplementation of PAA at an exploratory concentration slightly but significantly reduced Th17 cell frequencies in the lupus mice. The optimal effective PAA concentration and the mechanisms by which it regulates colonic immune responses in lupus remain to be elucidated; however, it is likely that PAA acts in concert with other microbial products, such as indole derivatives and BAs, to synergistically rebalance the Treg/Th17 responses and contribute to intestinal immune regulation.

It is well recognized that the loss of immune regulation is a central process that drives autoimmune response in SLE⁸⁸. Recent studies have shown that gut microbial-specific Th17 cells transdifferentiate into migratory T follicular helper (Tfh) cells and promote systemic autoimmune responses⁸⁹. Thus, the regain of intestinal Tregs and restriction of Th17 cell expansion in lupus-prone mice treated with UT1, potentially due to the modulation of gut microbiome functions, may contribute to the amelioration of systemic autoimmune activation, leading to reduced autoantibody production and improved renal pathology.

In summary, our results provide critical insights into the functions of the lupus-associated microbiome and uncover protective microbiome signatures associated with *F. prausnitzii*, mainly sustained carbohydrate catabolism, reprogrammed tryptophan metabolism, and enhanced BA modification, suggesting that these pathways mediate the contribution of the dysbiotic microbiome to lupus pathogenesis. Thus, our findings identify a probiotic modulator that may aid the design of microbiota-targeted therapeutic strategies for SLE management.

Method

Mice and treatment

B6.*Sle1*.Yaa mice have been previously described^{27,28}. Age-matched B6.*Sle1*.Yaa and C57BL/6J control male mice were used in this study. *F. prausnitzii* UT1 was cultured, and live bacterial stocks were prepared as described previously²⁵. Cohorts of B6.*Sle1*.Yaa mice were gavaged every 2 days with UT1 (10^9 CFU in 100 μ l PBS) or 100 μ l PBS for 2 or 3 months. Mice were euthanized 2 days after the last gavage. For PAA supplementation, phosphonoacetic acid (Thermo Scientific) was dissolved in drinking water (1 mg/ml), and the pH was adjusted with NaOH to match that of control water. B6.*Sle1*.Yaa mice were given PAA-supplemented or control drinking water *ad libitum* starting at 3 months of age until study termination at 5 months of age. Mice were bred and maintained under specific-pathogen-free conditions with a 12-h light/12-h dark cycle. Mice were euthanized by isoflurane anesthesia followed by cervical dislocation. All procedures were conducted in compliance with protocols approved by the University of Texas Health San Antonio IACUC under protocol numbers 20230051AR and 20220063AR.

16S rRNA sequencing

Fecal samples were collected from B6.*Sle1*.Yaa mice before treatment (week 0) and at weeks 4, 8, and 12 post-treatment. Fecal genomic DNA was extracted, and 16S rRNA libraries were constructed as described previously⁹⁰. Samples were sequenced to a depth of >81,803 paired-end reads (2 $\times$ 300 bp) per sample using the Illumina MiSeq instrument. Sequence reads were merged, quality-trimmed, and taxonomically classified using QIIME2 (v2022.8). Briefly, after denoising using DADA2 and removal of PCR artifacts, a minimum of 66,553 reads/sample was retained for taxonomic clustering using Greengenes 13.8 with 97% sequence similarity. Bacterial α - and β -diversities were determined using the Shannon index and Bray–Curtis distance, respectively.

Metagenomics profiling

Shotgun metagenomics sequencing was conducted for the fecal samples collected from B6.*Sle1*.Yaa mice treated with UT1 for 12 weeks, or B6.*Sle1*.Yaa and B6 controls. DNA libraries were constructed using the Illumina DNA Prep kit as described previously^{25,91}. Sequencing was performed on the Illumina NovaSeq X plus platform at the University of Florida NexGen DNA Sequencing Core Facility (ICBR; RRID:SCR_019152), yielding an average of 50.2 million paired-end reads per sample (2 $\times$ 150 bp). For the Asian human SLE cohort, one SLE sample, for which only one read of the paired-end sequencing was retrieved, was excluded from the analysis. For the U.S. cohort, single-end reads from visit 1, corresponding to untreated patients, were included in the analysis. Sequence reads were mapped to the mouse (GRCm38) or human (GRCh38) genome using bowtie2, and unmapped read pairs (clean microbial reads) were subjected to taxonomic profiling using the MetaPhlAn4 pipeline (v4.1.1), which relies on approximately 5.4 million clade-specific marker genes derived from ~1 million microbial genomes spanning 26,970 SGBs. The unclassified SGBs were annotated to Genome Taxonomy Database (GTDB) taxonomic profiles using mpa_vJun23_CHOCOPhlanSGB_202307_SGB2GTDB.tsv from MetaPhlAn4. Linear discriminant analysis effect size (LEfSe) was performed to identify bacterial species that significantly (LDA score > 2) contributed to compositional differences.

Metagenomes were functionally profiled using HUMAnN3⁹² to quantify genes and pathways. Briefly, based on identified microbial species from taxonomic profiling for each sample, reads were recruited to sample-specific pangenomes. Unmapped reads were aligned against UniRef90 using DIAMOND translated search⁹³. Search hits were weighted by alignment quality and sequence length to estimate the abundance of gene families, which were further combined into structured pathways from MetaCyc⁹⁴.

CAZyme mapping and substrate prediction were conducted as previously described²⁵. Briefly, the clean microbial reads were de novo assembled using MEGAHIT (v1.2.9)²⁵, keeping contigs with a minimal length of 1000 bp. The contigs were then passed to Prokka (v1.14.6) for gene annotation. CAZymes and CGCs were annotated based on the dbCAN3 database²⁹. Glycan substrates for CAZymes and CGCs were predicted using dbCAN-sub and dbCAN-PUL, respectively. The clean reads were mapped to the nucleotide coding sequences of proteins to calculate the abundance of the CAZymes and CGCs. TPM (Transcripts Per Million) was used as a measurement of the normalized DNA sequencing reads mapped to CAZymes and CGCs, as described in ref. 95.

metaT analysis

Fecal samples (2–3 pellets) were collected from B6.*Sle1*.Yaa mice gavaged with UT1 or PBS for 12 weeks. Fecal total RNA was extracted using the Quick-RNA Fecal/Soil Microbe Microprep Kit (Zymo Research), with an on-column DNase I digestion to remove DNA contaminants. About 300 ng RNA was used for rRNA depletion and cDNA library construction using the Illumina Stranded Total RNA Prep Ligation with Ribo-Zero Plus kit per manufacturer's instructions. Illumina NovaSeq yielded an average of 51.2 million paired-end raw reads (2 $\times$ 150 bp) per sample and 15.3 million mRNA reads per sample after removing reads of host origin and reads mapping to the default rRNA database (smr_v4.3_default_db) using SortMeRNA⁹⁶. The clean microbial mRNA reads were then used for metaT taxonomic and functional profiling, as well as CAZyme annotation and substrate prediction as described above. The activities of gene and CAZyme families were further assessed by comparing metaT RNA abundances versus metagenomic DNA abundances of the same samples.

Metabolomics analysis

Fresh fecal pellets were collected from the same UT1- or PBS-treated B6.*Sle1*.Yaa mice used for metaT and immediately frozen for

metabolite extraction. Metabolites were analyzed at the Southeast Center for Integrated Metabolomics using LC-MS in both positive and negative ionizations^{4,97}. Metabolite features were normalized to total ion chromatograms, and intensity differences between UT1 and PBS groups were evaluated using an unpaired Student's *t*-test. Metabolites were identified by comparison to the metabolomic library of purified standards. Metabolic pathway analysis was performed using *Mummichog* v2.6.1. The pathways represented by at least 2 significant metabolites in positive or negative mode are presented.

Isolation of immune cells and flow cytometry

Colonic cell isolation was performed as described previously⁹⁸. After collagenase digestion, single-cell suspensions of the colon were subjected to Percoll density gradient centrifugation for lymphocyte enrichment⁹⁸, or directly used for DC staining (no Percoll density gradient centrifugation)⁹⁹. Spleens were mechanically dissociated and passed through a 70- μ m cell strainer to generate single-cell suspensions. Mouse FcR Blocking Reagent (Miltenyi Biotec) was used to block non-specific binding to Fc receptors before surface staining. For cytokine staining, cells were stimulated with 50 ng/ml PMA and 500 ng/ml ionomycin for 4 hours and Brefeldin A (1X; Thermo Fisher Scientific) for 2 hours. The live and dead cells were discriminated by Live/Dead Fixable Aqua or Violet Dead Cell Stain Kit (Thermo Fisher). Cells were first stained for cell-surface markers and then resuspended in fixation/permeabilization solution [FoxP3/Transcription Factor Staining Buffer kit (Cytek)] for intracellular staining. Cells were stained with a cocktail of fluorescent antibodies specific for: myeloid cells, T cells, and B cells. Flow cytometric gating strategies are provided in Supplementary Fig. 8. Antibodies were listed in Supplementary Table 1. Sample acquisition was performed using SpectroFlo (v3.3.0) software on a Cytek Northern Lights flow cytometer and analyzed using FlowJo software (v10.10). Correlations between the number of immune populations and fecal metabolites were assessed in the correlation matrix based on Spearman's rank correlation tests. The correlation matrix was calculated using the *rcorr()* function of the R package Hmisc, and *p* values were calculated with the *rcorr.adjust()* function with correction for multiple testing (method "fdr").

qPCR analysis

Total RNA was extracted from distal colons (~0.5 cm in length) or ~10 million splenocytes using Trizol LS reagent (Invitrogen)⁹⁰. The top aqueous phase was further purified using the Aurum Total RNA Mini Kit (Bio-Rad) with an on-column DNase I digestion step to completely remove gDNA contamination. cDNA was synthesized using iScript Advanced cDNA Synthesis Kit (Bio-Rad), and qRT-PCR was performed with PowerUp SYBR Green Master Mix (Thermo Fisher Scientific) on a QuantStudio 6 Pro real-time PCR system (Thermo Fisher Scientific). Relative gene expression was determined using the $2^{-\Delta\Delta C_T}$ method with *RplO* as the reference gene, and data were normalized to the mean expression in the PBS-treated B6.*Sle1*.Yaa group. For UT1 colonization, the fecal abundance of *F. prausnitzii* was quantified using species-specific 16S rRNA primers and normalized to the total bacterial abundance amplified using universal 16S rRNA primers. Primer sequences are listed in Supplementary Table 2.

Renal pathology

Paraformaldehyde-fixed paraffin kidney sections were stained with periodic acid Schiff (PAS). The type and extent of renal lesions were evaluated using a modification of the International Society of Nephrology and Renal Pathology Society classification of lupus nephritis and the NIH activity and chronicity indices in a blind manner. Renal parenchymal components, including glomeruli, vessels, tubules, and interstitium, distributed throughout the renal sections, were assessed. At least 15 glomeruli per kidney were examined for the presence of mesangial expansion, mesangial hypercellularity, crescents,

and glomerulosclerosis. Tubular dilatation, and tubular casts were quantified on a scale of 1–4. Renal pathology scores were calculated as the sum of the 5 criteria. IgG2c and C3 immune complexes were detected in frozen sections as previously described⁶⁸. Imaging and quantitation were performed with a Keyence microscope Model BZ-X810 using the image stitching module.

Antibody measurements

Serum anti-dsDNA IgG was detected by ELISA in sera diluted 1:100 as previously described⁷⁴. The same protocol was applied for anti-dsDNA IgG2c, except the secondary antibody was alkaline phosphatase-conjugated goat anti-mouse IgG2c (SouthernBiotech, catalog 1081-04; 1:1000 dilution).

Statistical analysis

Statistics were performed using GraphPad Prism software. Unless otherwise specified, differences between groups were evaluated using unpaired 2-tailed Student's *t*-test (2 groups), ordinary one-way ANOVA with Tukey's correction, or Welch ANOVA with Dunnett T3 multiple testing correction (3 groups), as indicated in the figure legends. Data are presented as mean $\pm$ standard errors (SD). *p* < 0.05 was considered significant.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The metagenomic and metaT raw FastQ files have been made publicly available under the NCBI BioProject accession number [PRJNA1263124](https://www.ncbi.nlm.nih.gov/bioproject/PRJNA1263124). Raw and processed fecal metabolomics data have been deposited in the National Metabolomics Data Repository (NMDR) via the Metabolomics Workbench under study ID [ST004311](https://www.metabolomicsworkbench.org/study/ST004311). Previously published fecal metagenomics data from human SLE patients are available under NCBI BioProject accession numbers [PRJNA532888](https://www.ncbi.nlm.nih.gov/bioproject/532888) (Asian cohort; <https://www.ncbi.nlm.nih.gov/bioproject/532888>) and [PRJNA156897](https://www.ncbi.nlm.nih.gov/bioproject/PRJNA156897) (U.S. cohort; <https://www.ncbi.nlm.nih.gov/bioproject/?term=PRJNA156897>). Source data are provided with this paper.

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Competing interests

The authors declare no competing interests.

Additional information

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