

Exploratory multi-omics analysis reveals host-microbe interactions associated with disease severity in psoriatic skin

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Summary

Background Psoriasis (Pso) is a chronic inflammatory skin disease that poses both physical and psychological challenges. Dysbiosis of the skin microbiome has been implicated in Pso, yet a comprehensive multi-omics analysis of host-microbe interactions is still lacking. To bridge this gap, we conducted an exploratory study by adopting the integrated approach that combines whole metagenomic shotgun sequencing with skin transcriptomics.

Methods This was a cross-sectional study, adult patients with plaque-type Psoriasis (Pso) and healthy volunteers were included. Skin microbiota samples and biopsies were collected from both lesional and non-lesional skin areas on the lower back. Weighted Gene Correlation Network Analysis (WGCNA) was employed for co-expression network analysis, and cell deconvolution was conducted to estimate cell fractions. Taxonomic and functional features of the microbiome were identified using whole metagenomic shotgun sequencing. Association between host genes and microbes was analyzed using Spearman correlation.

Findings Host anti-viral responses and interferon-related networks were identified and correlated with the severity of psoriasis. The skin microbiome showed a greater prevalence of *Corynebacterium simulans* in the PASI severe-moderate groups, which correlated with interferon-induced host genes. Two distinct psoriatic clusters with varying disease severities were identified. Variations in the expression of cell apoptosis-associated antimicrobial peptides (AMPs) and microbial aerobic respiration I pathway may partly account for these differences in disease severity.

Interpretation Our multi-omics analysis revealed for the first time anti-viral responses and the presence of *C. simulans* associated with psoriasis severity. It also identified two psoriatic subtypes with distinct AMP and metabolic pathway expression. Our study provides new insights into understanding the host-microbe interaction in psoriasis and lays the groundwork for developing subtype-specific strategies for managing this chronic skin disease.

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Research in context

Evidence before this study

Previous research has suggested that dysbiosis of the skin microbiome plays a role in psoriasis. Several studies have shown that the diversity of microbiota in psoriatic skin differs from that in healthy skin, particularly regarding Actinobacteria and Firmicutes. However, most of these studies rely on amplicon sequencing, which offers relatively low resolution at the species level and lacks microbial functional information. Additionally, these studies do not include an integrated analysis of the skin microbiome and host gene interactions.

Added value of this study

Our study expands current knowledge by adopting a multi-omics approach, which combines whole metagenomic shotgun sequencing with skin transcriptomics, to explore the relationship between the host and skin microbiota. We observed that anti-viral responses and interferon-related

networks correlated with disease severity. *Corynebacterium simulans* was highly prevalent in PASI severe-moderate skin and correlated with interferon-related host genes. Further analysis, based on microbial functional features, identified two distinct disease clusters. The differences in cell apoptosis-associated antimicrobial peptides (AMPs) and the microbial aerobic respiration I pathway may partly explain the varying disease severity between these clusters.

Implications of all the available evidence

Our findings underscore the critical role of anti-viral responses and *Corynebacterium simulans*, along with their interaction, in the severity of psoriasis. Moreover, the identification of two distinct disease clusters with varying microbial and host features may provide insights into developing novel, personalized disease management strategies for psoriasis patients.

Introduction

Psoriasis (Pso) is a prevalent systemic inflammatory disease that affects about 1%–3% of the population worldwide and can cause varieties of comorbidities, such as psoriatic arthritis (PsA), cardiovascular disease, and type 2 diabetes.^{1,2} Based on distinct disease characteristics, Pso is divided into clinical subtypes, with plaque psoriasis being the most common. Multiple factors have been found to be involved in the development and progression of Pso, including the immune system, the epidermal barrier, and environmental factors, such as medications, trauma and streptococcal infection.³ So far, there is no well-established cure for psoriasis, and it causes significant economic and psychological burden for individuals and societies.⁴

Skin is the home of an extensive microbiota, which may also contribute to disease. Psoriasis skin microbiome vary in diversity and composition compared to healthy skin.⁵ Studies have also indicated that the relative abundance of Actinobacteria, Firmicutes, and Proteobacteria differs in psoriatic skin when compared to healthy skin microbiota.^{6–8} For example, while *Cutibacterium acnes* is prevalent in healthy skin, it is reduced in abundance in psoriatic skin, making room for other taxa like *Streptococcus*.^{9,10} Interleukin (IL)-23/Th17 axis plays a pivotal role in the hyperproliferation of keratinocytes.^{11–13} In turn, the hyperproliferative keratinocytes release high levels of AMPs and cytokines, resulting in a positive feedback loop that further facilitates the progression of psoriatic symptoms.¹⁴ Therefore, host-microbes interaction may be involved in the development of psoriasis via the activation of distinct signaling pathways.¹⁵ *Streptococcus* infection was found

to be associated with psoriasis flares in some patients, along with the T cells activation through Streptococcal peptidoglycan.^{16,17}

Although dysbiosis in the skin microbiome has been reported in psoriasis, research on the interaction between the host and microbiota using multi-layer omics data is lacking. Multi-omics analysis of Pso skin microbiome is reported only once, and information on host and skin microbial functional features in Pso is virtually non-existing.^{18,19} To better understand the interactions between host and microbes associated with psoriasis, we integrated omics data from whole metagenomic shotgun sequencing (WMS) and skin transcriptomics. We hypothesize that 1) Psoriasis can cause the differential expression of host genes and skin microbiome in Pso lesional skin sites compared to Pso non-lesional sites and healthy skin, which would be associated with disease severity. 2) The presence of distinct clusters of Pso patients and the differential abundance of host genes and skin microbial features. The data were collected from psoriatic lesional and non-lesional skin sites, as well as from the skin of healthy volunteers, utilizing the clinically well-characterized MAARS (Microbes in Allergy and Autoimmunity Related to the Skin) cohort. We aimed to study the factors associated with the severity of psoriasis (Pso) by comparing psoriatic lesional samples to Pso non-lesional samples and healthy volunteers using serial multi-omics analysis of skin microbiome and transcriptome. The objectives of this study are: 1) To determine the differential expression of host genes and their association with disease severity in psoriatic skin sites; 2) To investigate the skin microbes and their

interactions with host genes in the pathogenesis and development of Pso; 3) To detect whether there are distinct clusters of Pso based on the expression of host genes, microbial features, and their associations. Our work reveals host genes, microbial features, and host-microbes interaction associated with the psoriasis pathobiology and disease severity.

Methods

Study subjects and design

This was a cross-sectional study using the clinically well-defined European MAARS (Microbes in Allergy and Autoimmunity Related to the Skin) cohort (<https://cordis.europa.eu/project/id/261366>). Subjects recruitment details have been previously described.²⁰ Metadata is shown in Table S1. Microbiome samples and skin biopsies were obtained from areas with active disease and adjacent non-lesional skin in the lower back in Pso patients. Healthy volunteers were sampled in the corresponding skin areas.

Patients (18–83 years) with plaque-type PSO as well as healthy volunteers were used in this study. Each subject underwent a physical examination by a dermatologist and the medical history was recorded. The diagnoses were made by a dermatologist based on clinical presentation, personal history, laboratory findings and the criteria of Hanifin and Rajka.²¹ Subjects with any of the following conditions were excluded: concurrent autoimmune diseases (such as rheumatoid arthritis, alopecia areata, diabetes, etc.); recent systemic antibiotic use within 2 weeks, and systemic immunosuppressive therapy; phototherapy, or systemic biologic agents within the preceding 12 weeks before screening. The patients or healthy volunteers who did not match these clinical exclusion criteria were removed from this study.

Skin biopsies, microbiome samples, and clinical parameters were collected from healthy volunteers (HV) with no Pso history and Pso patients, lesional and non-lesional skin were obtained from the lower back of the same patients. Prior to skin sampling, biopsy sites were left untreated for a minimum of 2 weeks, and only non-antibacterial Dove soap was permitted for cleansing, with no washing allowed for 24 h before sampling. Biological samples collected for analysis included: 1. microbiome samples from the lower back (Pso, HV), without prior cleaning or preparation of the skin surface using sterile gloves to prevent cross-contamination were obtained by placing a sterile ring (2.5 cm diameter) onto the appropriate skin area, 1.5 ml phosphate-buffered saline (PBS) was supplemented into the ring and the area sampled scraping a glass rod in a circular motion ten times to the left and to the right. Subsequently, the microbiome-enriched PBS was harvested and stored. In addition, mock samples containing only PBS were collected at each sampling time in order to assess contamination; 2.6 mm punch biopsies from the skin at

the “microbiome” sites were obtained. Subsequently, samples were stored in RNAlater (Sigma–Aldrich) and subjected to further analyses. Lower back was chosen for PSO lesions, at the same time taking care in minimizing harm due to the surgical procedure of obtaining skin biopsies. Samples from active skin disease, i.e., lesional skin, and adjacent non-lesional skin were included in the study, and normal skin from HV was used as a control. Samples from HV were taken from sites corresponding to those in Pso. Identical SOPs were used in all three clinical centers and quality and homogeneity were assessed and confirmed in a pilot study prior to starting the major sample collection.

RNA was isolated from skin biopsy samples, followed by transcriptional analysis using Affymetrix Human Gene 2.1 ST chips. Additionally, shotgun metagenomic sequencing was performed on DNA extracted from the microbiome samples. An exploratory study was then conducted by integrating data from multiple omics layers. Six Pso patients and one healthy volunteer did not meet the quality control standards for the microarray assay and were consequently excluded from the study. The final analysis included samples from 116 Pso patients and 102 healthy volunteers.

Ethics

The study was approved by the appropriate local Institutional Review Boards (University of Helsinki, Dnro 91/13/03/00/2011; Heinrich Heine University Düsseldorf, 3647/2011; King's College London, 11/H0802/6) and all subjects provided written informed consent before participation.

Weighted gene co-expression network analysis (WGCNA)

Gene expression data was extracted using package *affy* (v1.74.0) in R (v4.2.1) and used to identify the co-expression network modules by WGCNA package (v1.72.1).²² The *blockwiseModules* function was used to construct the network with the parameters *minCorKME* = 0.7 and *minKMEtoStay* = 0.5, and the soft power threshold was determined with the *pickSoft-Threshold* of the package. The module eigengene was calculated, and the correlation between individual gene expression and the module eigengene of a given module was defined as the module membership (MM). The correlation between gene expression profiles with clinical trait was determined as the gene significance (GS).

Enrichment analysis, protein-protein interaction (PPI) network generation

To understand the modules from the functional aspect. Functional annotation of the modules defined by WGCNA was conducted using *clusterProfiler* (v4.6.2) with the functions *enrichGo*,²³ and the adjust p value for cutoff was set as 0.05. PPI network of genes with MM >0.8 and GS >0.2 was generated on the website of

STRING (www.string-db.org, Version 11.5),²⁴ all networks with a PPI enrichment p-value <0.05 were included for visualization and hub genes identification. The network was visualized with Cytoscape software (v3.9.1).²⁵ The hub gene was identified by CytoHubba.²⁶ All the other graph visualization was conducted using ggplot2,²⁷ corrplot,²⁸ ggsci,²⁹ and ggpubr³⁰ in R (v4.2.1).

Leukocyte deconvolution analysis

CIBERSORTx is an online analytical tool to estimate the abundances of subset cell types using gene expression data.³¹ DerM22³² and LM22³³ gene signature matrices were used as gene signature reference in this analysis, DerM22 contains all major cell types that are present in the skin and LM22 include 22 different immune cells isolated from peripheral blood. The gene expression matrix from the microarray assay was used as input to estimate the cell fractions in Pso lesional, non-lesional samples, and healthy volunteers, and the estimations are based on 1000 permutations, the adjusted p-values of all the predicted cell fractions are less than 0.05.

Whole metagenomic shotgun sequences analysis

Raw reads were quality-trimmed as described previously.²⁰ Contaminating human sequences were removed using Bowtie2 v2.5.1³⁴ (Reference database: GRCh38, https://genome-index.s3.amazonaws.com/bt/GRCh38_noalt_as.zip) with default parameters. A total of 5819 million raw reads were generated, and after removing low-quality and human genome-associated sequences, 1158 million clean reads were obtained for further analysis.

We used MetaPhlAn 4.0³⁵ and HUMAnN 3.0,³⁶ respectively to obtain the microbial taxonomy and functional features. Briefly, the shotgun metagenomic sequences were mapped to clade-specific markers to identify the taxonomy using MetaPhlAn 4.0, and the nucleotide level pangenome mapping was conducted via Bowtie2 v2.5.1 with reference to the ChocoPhlAn database (humann_databases -download chocophlan full/path/to/databases), the translated search was done for the unmapped reads through DIAMOND v2.0.430³⁷ against the UniRef90 universal protein reference database (humann_databases -download uniref uniref90_diamond/path/to/databases), then the generated gene list was referred to the Metacyc database³⁸ (<https://metacyc.org/>) for pathway collection and regrouped to level-4 enzyme commission (EC) categories. Data of Functional features was normalized to relative abundance, and the taxonomy data was normalized based on cumulative-sum-scaling (CSS) using metagenomeSeq R package, and logarithm transformation was applied for further analysis.³⁹

Profiling of clusters by clustering analysis

Using the UniRef90 gene families obtained from the whole metagenomic shotgun sequences analysis of Pso lesional group as input matrix, the hierarchical

clustering was performed via package tidymodels (v1.1.0)⁴⁰ and cluster (v2.1.4)⁴¹ in R to identify the different clusters among the Pso patients. The agglomerative coefficient (AC) was calculated by cluster::agnes() function to select the most stable clustering method, in this study the ward linkage was computed. Silhouette analysis which indicates the separation distance between the clusters estimated two clusters present in our dataset.⁴² Silhouette coefficient was calculated via the fviz_nbclust function in factoextra (v1.0.7) R package.⁴³ The hierarchical dendrogram was cut into two clusters through the cutree function from stats package (v4.2.1).⁴⁴

Statistics

Data matrices from metagenomic profiles and host genes were imported into R (v4.2.1). The statistical power analysis using micropower,⁴⁵ a simulation-based method for permutational multivariate analysis of variance (PERMANOVA)-based β -diversity comparisons, to assess the effect size and statistical power of this study with 116 Pso patients and 102 healthy volunteers. The study has a power of 0.8 to detect an effect size (adjusted coefficient of determination ω^2) of 0.002, with a significance level of 5%, and a power of 0.9 to detect an effect size of 0.003, with a significance level of 5%. Unless otherwise stated, analysis was performed using a Mann–Whitney test to compare two groups and Kruskal–Wallis test for more than two groups. p-values were adjusted with the Benjamini–Hochberg method for multiple hypothesis testing, and adjusted p-values < 0.05 were set as the threshold for a significant difference. The partial Spearman correlation was conducted to adjust age and gender using R package ppcor (v1.1)⁴⁶ and visualized using the corrplot package (v0.92),²⁸ the circus plot was generated by circlize (v0.4.15)⁴⁷ R package. Multivariable association in microbiota and phenotypes was conducted by MaAsLin2 (v1.10.0),⁴⁸ accounting for age, gender, batch, and clinic. The distance-based Redundancy analysis (dbRDA) was performed by dbrda function in the R package vegan (v2.6.4).⁴⁹ Heatmaps were generated using the pheatmap package (v1.0.12).⁵⁰

Role of funders

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Co-expression networks identify psoriasis-associated gene modules

Gene expression profiles were assessed for psoriasis patients including lesional site and non-lesional site from the same patient, and healthy individuals. The study outline is summarized in Fig. 1. Skin transcriptome of Pso lesional samples were highly distinct

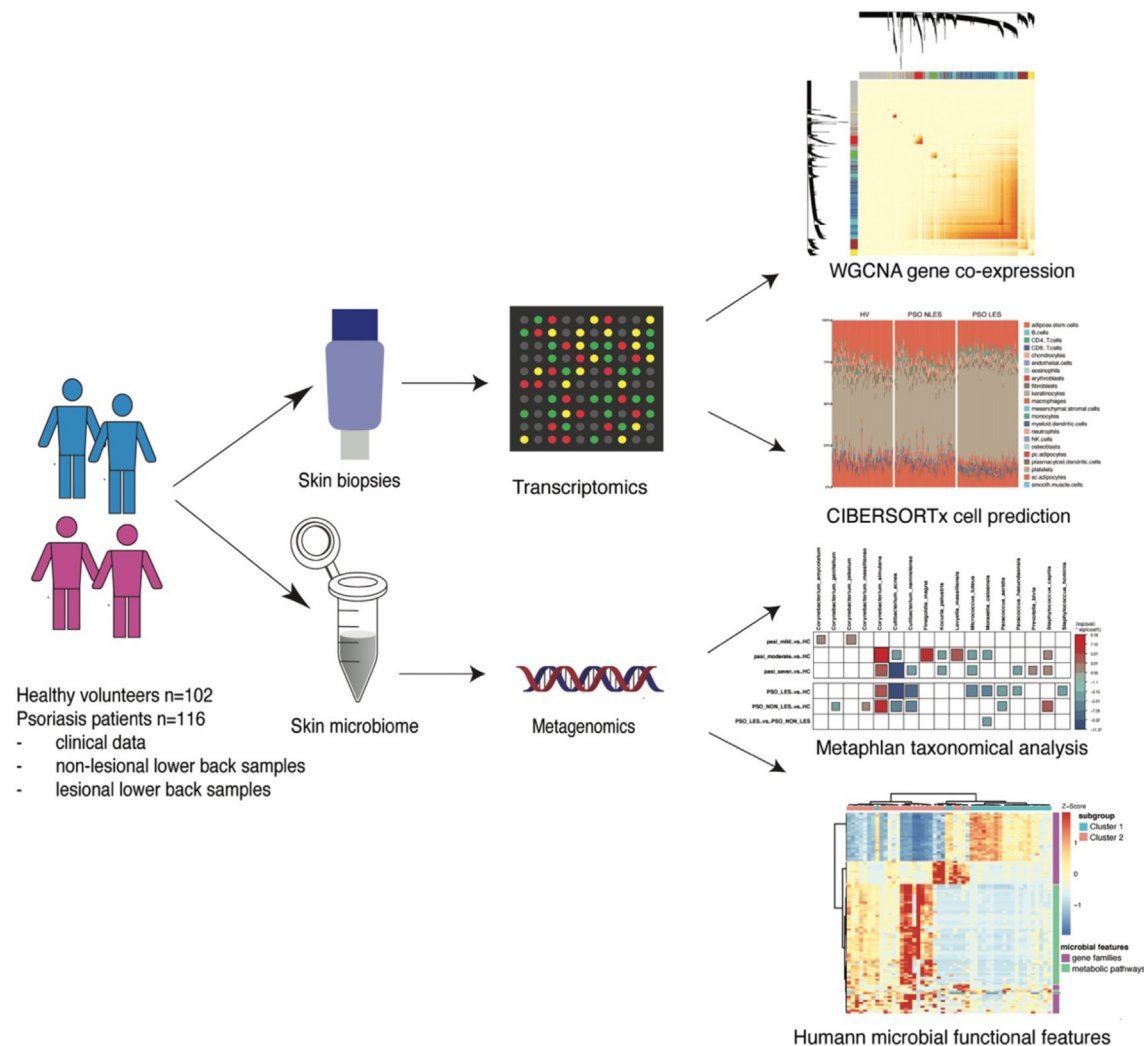


Fig. 1: Study outline. Skin tissues and microbiome samples were collected from psoriasis patients and healthy volunteers. Microbial species and functional features were generated using whole-genome metagenomic shotgun sequencing. Gene co-expression and cell fraction matrices were generated using transcriptomic data derived from microarray assays. Integration analysis was performed across different omics layers to better understand host-microbe interactions during the pathogenesis of psoriasis.

from the non-lesional samples and healthy skin (Figure S1). To further investigate the gene expression profiles and correlate them with the clinical parameters, weighted gene correlation network analysis (WGCNA) was utilized to detect the co-expressed genes as different modules. Within the whole cohort, WGCNA identified six modules that were annotated with GO terms (Fig. 2A and B). Among these six modules, module turquoise was positively associated with lesional skin and disease severity (PASI score) (Fig. 2C) and was enriched in inflammation-related functional pathways, such as leukocyte cell adhesion, the positive regulation of cytokine production and defense response to virus (Fig. 2B). To further investigate this module, the GS (genes correlation with clinical groups), and module membership

(MM) were calculated, and the central genes with $MM > 0.8$ and $GS > 0.2$ were used to generate the protein-protein interaction (PPI) network. Central genes showed predicted protein-protein interactions, including cell cycle and interferon (IFN) response sub-networks (Fig. 2D).

In parallel, WGCNA was conducted separately on the healthy volunteers in conjunction with the Pso non-lesional samples, as well as on the lesional samples alone. The gene co-expression analysis of healthy volunteers and the Pso non-lesional group revealed six modules (Figure S2A). The GO term functional analysis for each module showed distinct functional properties, summarized in Figure S2B. We then analyzed the module genes in the lesional samples and discovered a

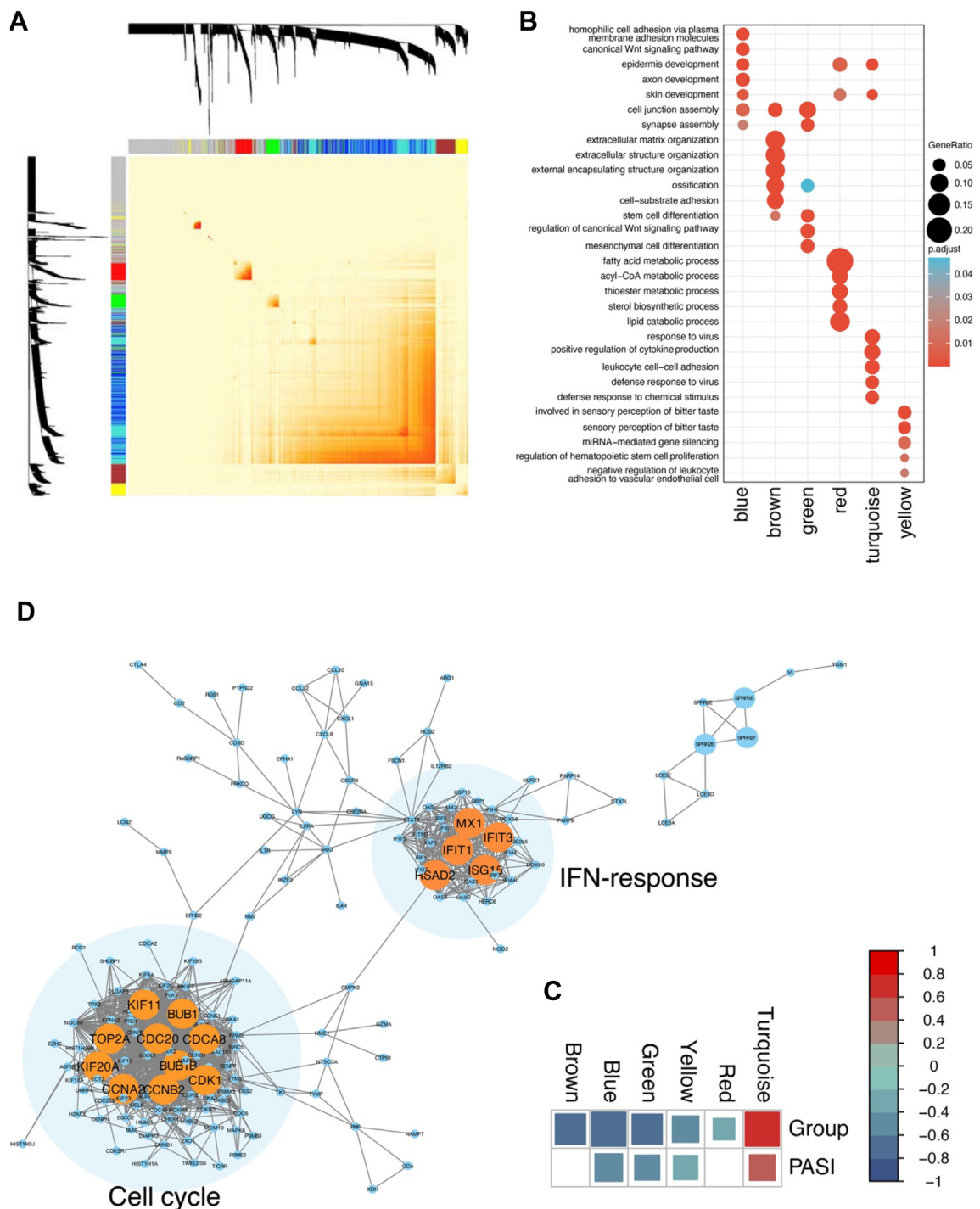


Fig. 2: Gene co-expression network construction for psoriasis lesional, non-lesional, and healthy volunteers. (A) Topological overlap matrix plot and the cluster dendrogram of 1000 randomly selected genes. This plot displays the correlation degree of each module. (B) Modules were further analyzed for functional enrichment using Gene Ontology (GO). (C) Modules were associated with clinical traits. The color indicates the correlation coefficient. Only correlations with a p-value < 0.001 are displayed. (D) Modules that correlated positively with the traits were further examined for Protein-Protein Interaction (PPI) networks using the STRING database (V11.5) and visualized with Cytoscape. Hub genes detected by CytoHubba are highlighted in orange. All PPI networks exhibited an enrichment value of $p < 1 \times 10^{-10}$.

different expression pattern among samples from lesional skin (Figure S2C). The red module was positively correlated with the lesional group and was enriched in functions related to lymphocyte differentiation and T-cell activation (Figure S2D). For the lesional group alone, eight modules were identified through WGCNA analysis (Figure S3A), and the GO term annotations for each module are displayed in Figure S3B. Upon examining the module genes from the healthy volunteers and the Pso non-lesional group, a distinct expression pattern emerged when compared to the lesional subjects (Figure S3C). The blue, pink, and yellow modules were positively correlated with the lesional skin and were associated with leukocyte involvement and the cell cycle (Figure S3D).

WGCNA analysis and gene correlation with PASI score reveal anti-viral response associated with disease severity in Pso

To further investigate the variations of host genes in relation to Pso severity, we conducted a Spearman

correlation analysis between host genes and the PASI score separately for the non-lesional only and lesional only groups. Host genes that exhibited significant correlations were subsequently annotated in GO terms. Functions related to the response to viral infections were identified in both the non-lesional-only and the lesional-only Pso groups (Fig. 3A and B). Additionally, IFN-associated networks emerged from the PPI analysis in both datasets (Fig. 3C and D).

To gain a deeper understanding of the genes implicated in the progression and severity of the disease, we isolated the gene expression matrices derived from non-lesional and lesional skin of psoriasis patients separately. Subsequently, we extracted the top 15 and bottom 15 samples based on the rank of the absolute global PASI score. WGCNA analysis identified a total of seven modules in non-lesional and lesional groups respectively, which were assigned GO terms (Figure S4A and B). The brown module from non-lesional group, black, red, and turquoise modules from lesional group displayed a negative correlation with the PASI score, and

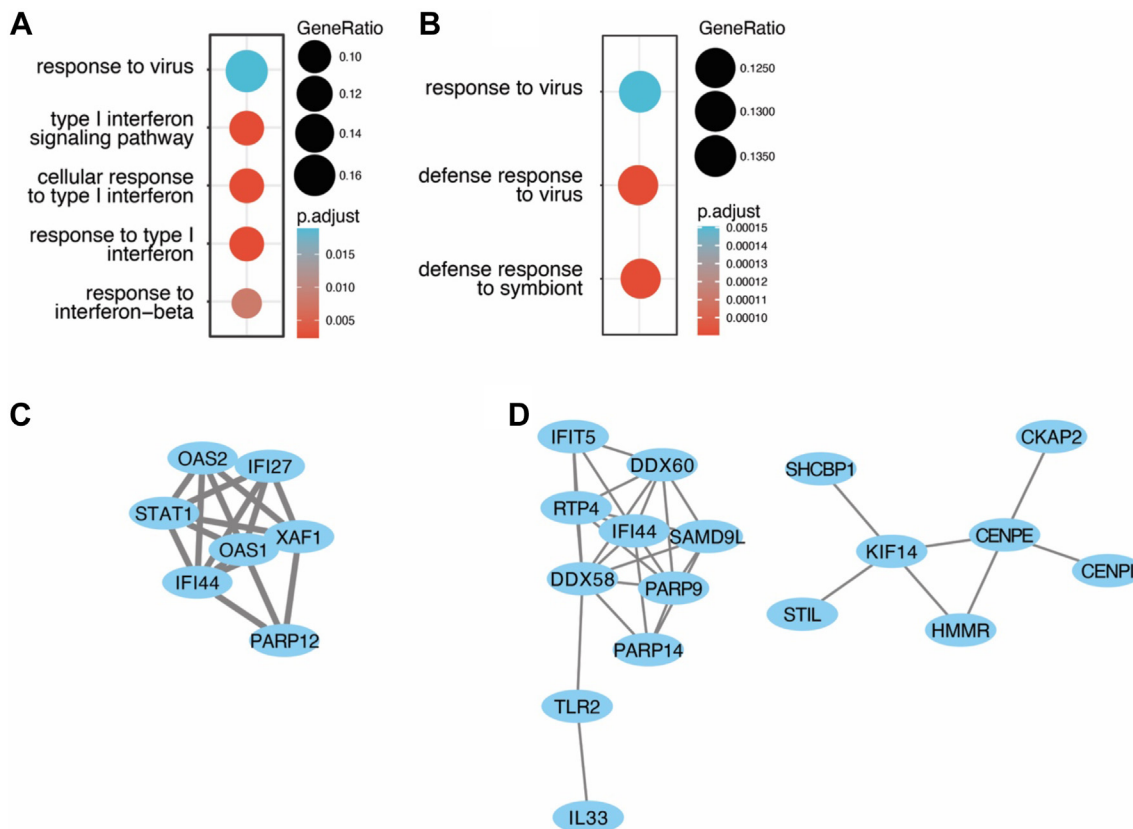


Fig. 3: Host genes correlated with PASI score in psoriasis non-lesional only and lesional only groups. Host genes correlating with the PASI score were further analyzed for functional enrichment using Gene Ontology (GO), by using host genes with absolute Spearman correlation coefficient >0.3 and p-value (FDR adjusted) <0.05 in the non-lesional only group (A) and by using host genes with p-value (FDR adjusted) <0.05 in the lesional only group (B). Protein-Protein Interaction (PPI) networks were generated using the same data matrix in the non-lesional only group (C), and the lesional only group (D), by using the STRING database (V11.5) and visualized with Cytoscape. All PPI networks displayed an enrichment value of $p < 1 \times 10^{-10}$.

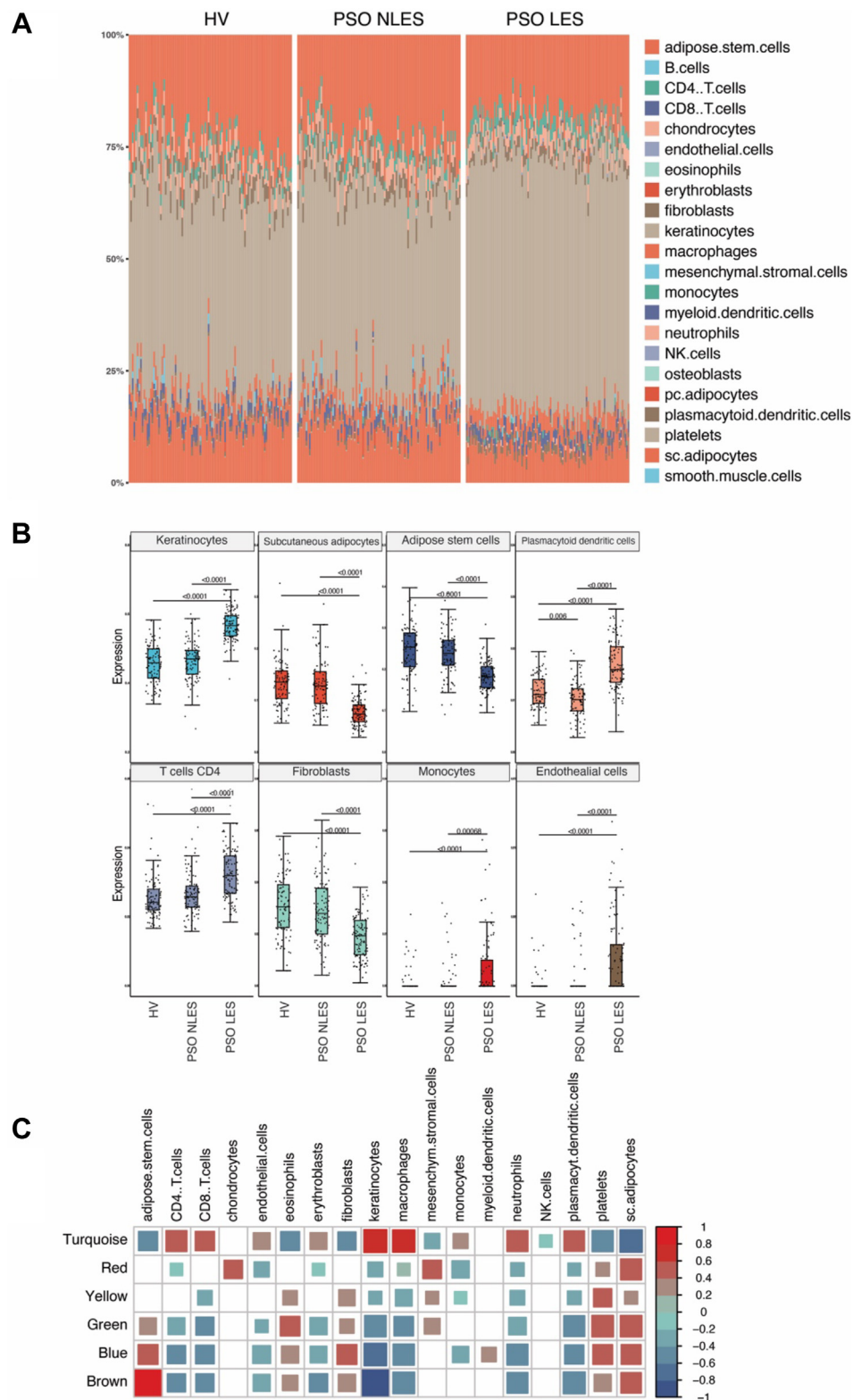


Fig. 4: Leukocyte composition and correlation with gene co-expression modules. (A) Prediction of cell fractions from the microarray gene expression matrix was done using CIBERSORTx. The DerM22 cell signature database served as the reference. (B) Boxplots depict differences in

the brown and red modules were both associated with sodium ion transport pathway (Figure S4C and D).

Pso alters blood leukocyte composition, and is correlated with the gene co-expression modules

Next, we employed Cibersort, a leukocyte deconvolution algorithm, to identify cellular changes associated with Pso based on the cutaneous transcriptomes. DerM22, which encompasses major skin cell types, served as the reference signature matrix. Cell fractions associated with lesional psoriatic skin differed significantly from those of non-lesional psoriatic skin and healthy skin. Notably, the algorithm predicted an increase in keratinocytes, CD4 T cells, monocytes, plasmacytoid dendritic cells, and endothelial cells, along with a decreased occurrence of subcutaneous adipocytes, adipose stem cells, and fibroblasts in lesional psoriatic skin. The result suggested hyperkeratosis and ongoing immune reactions driven by innate and adaptive immune responses at the lesional site (Fig. 4A and B).

The cell fractions were further used for downstream association analysis with gene modules derived from WGCNA of all samples. The module turquoise was positively correlated with the CD4 T cells and keratinocytes, macrophages, monocytes, neutrophils, and plasmacytoid dendritic cells, further indicating an important role of these leukocyte subsets in Pso (Fig. 4C).

In addition, we also utilized the LM22 signature matrix for Cibersort analysis. In line with the result derived from the DerM22, the estimated cell fractions from LM22 revealed that lesional Pso skin is distinct from the healthy skin and non-lesional skin (Figure S5A). The predicted levels of dendritic cells, activated CD4 memory cells, and monocytes were markedly elevated in the Pso lesional group. These cell fractions correlated with the turquoise module, suggesting a significant change in the immune system response associated with Pso (Figure S5B and C).

C. simulans is enriched in psoriatic lesional skin and associated with host genes related to psoriasis pathomechanisms

To identify microbial species related to the disease severity in psoriasis, we conducted a multivariable association analysis using MaAsLin2. We found 13 species enriched in three PASI categories (i.e., mild, moderate and severe), and 11 species that were significantly associated with disease lesion (Fig. 5A). Among these species, the abundance of *C. simulans* was increased in PASI moderate and PASI severe, lesional and

non-lesional groups compared with healthy skin. In contrast, *C. acnes* was decreased in these groups (Fig. 5B). Subsequent analysis assessed the correlation of *C. simulans* and *C. acnes* with the estimation of leukocyte compositions derived from Cibersort. *C. simulans* positively correlated with the estimated abundance of keratinocytes, CD4 T cells, and dendritic cells, whereas *C. acnes* exhibited the opposite trend (Fig. 5C).

Since the turquoise module from the WGCNA analysis of the entire data showed association with psoriatic lesional skin, we further correlated the transcriptome with the skin microbiome. By integrating the abundance of microbial species related to the PASI severe and Pso lesional and Pso nonlesional skin, with the expression of central host genes of turquoise module, we uncovered significant interactions between cutaneous gene expression and skin microbiome in psoriasis. The abundance of *C. simulans* and *C. acnes* were significantly correlated with the expression of several central host genes (Fig. 5D). Notably, we found that interferon-inducible genes, such as IFIH1 and IFI27, were associated with the abundance of these two species.

Microbial gene family analysis reveals two psoriasis clusters with distinct microbial and host features

The dbRDA analysis showed that microbial functional features significantly differed between psoriatic lesional and nonlesional skin as well as healthy skin in terms of microbial species (Figure S6A) and UniRef90 gene families (Figure S6B). Given the heterogeneity of psoriasis, we hypothesized the presence of additional distinct endotypes of psoriasis based on skin microbiome (functional potential). To investigate this further, we conducted a hierarchical clustering analysis using microbial gene families and identified two distinct clusters, cluster 1 ($n = 24$) and cluster 2 ($n = 26$), within the lesional Pso group (Fig. 6A). Silhouette analysis further confirmed that two clusters were the optimal number for further analysis (Figure S7). Using microbial features and host gene expression as input, we performed a differential analysis with limma ($v3.52.4$).⁵¹ We found several microbial features and host genes to be dissimilar between cluster 1 and cluster 2 (Fig. 6B and C).

The abundance of *Micrococcus luteus* was lower in lesional psoriatic skin compared with non-lesional psoriatic and healthy skin, as well as in cluster 1 compared with cluster 2 (Fig. 6B). Beyond taxonomic features,

immune cell expression deconvoluted via the Cibersort (CS) algorithm, comparing PSO lesional to both non-lesional and healthy volunteers. Within each boxplot, horizontal lines denote median values; boxes extend from the 25th to the 75th percentile of each group's distribution of values. (C) Gene co-expression modules were associated with cell fractions. The color indicates the correlation coefficient. Only correlations with a p -value < 0.001 are displayed. PSO LES, psoriasis lesional skin; PSO NLES, psoriasis non-lesional skin; HV: healthy volunteer.

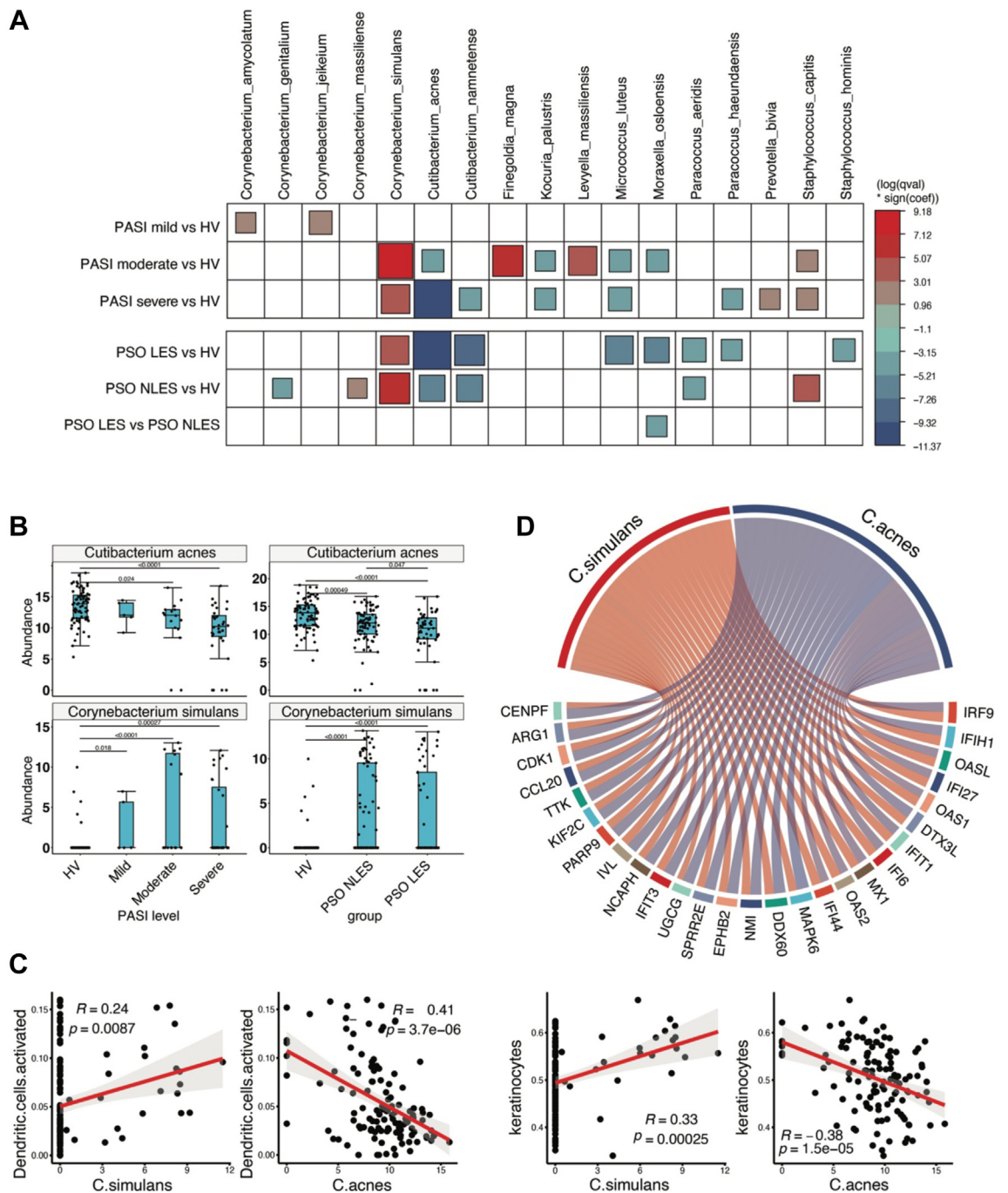


Fig. 5: *C. simulans* is enriched in psoriatic lesional skin and associated with host genes related to psoriasis pathomechanisms. (A) The association between skin microbiota and PASI score levels (upper), as well as clinical groups (lower), is presented. This association was assessed using multivariate analysis by linear models (MaAsLin; FDR < 0.05). The size and shading of the squares indicate the magnitude of the association. PSO LES, psoriasis lesional skin; PSO NLES, psoriasis non-lesional skin; HV: healthy volunteer. PASI mild: PASI score < 7, PASI moderate: 6 < PASI score < 11, and PASI severe: PASI score > 10. See also [Figure S6A](#). (B) Boxplots display differences in *C. simulans* and *C. acnes* across varying PASI levels and clinical groups. Within each boxplot, horizontal lines denote median values; boxes extend from the 25th to the 75th percentile of each group's distribution of values. (C) The Spearman correlation between *C. acnes* and *C. simulans* with immune cells derived from the Cibersort analysis. The grey shadow refers to the 95% confidence interval. (D) The association between the abundance of *C. simulans* and *C. acnes* with the central genes of the turquoise module is shown. The width of edges was proportional to the correlation coefficient, where blue lines indicate inverse correlations and red lines indicate positive correlations. Only edges with a p-value < 0.05 are displayed.

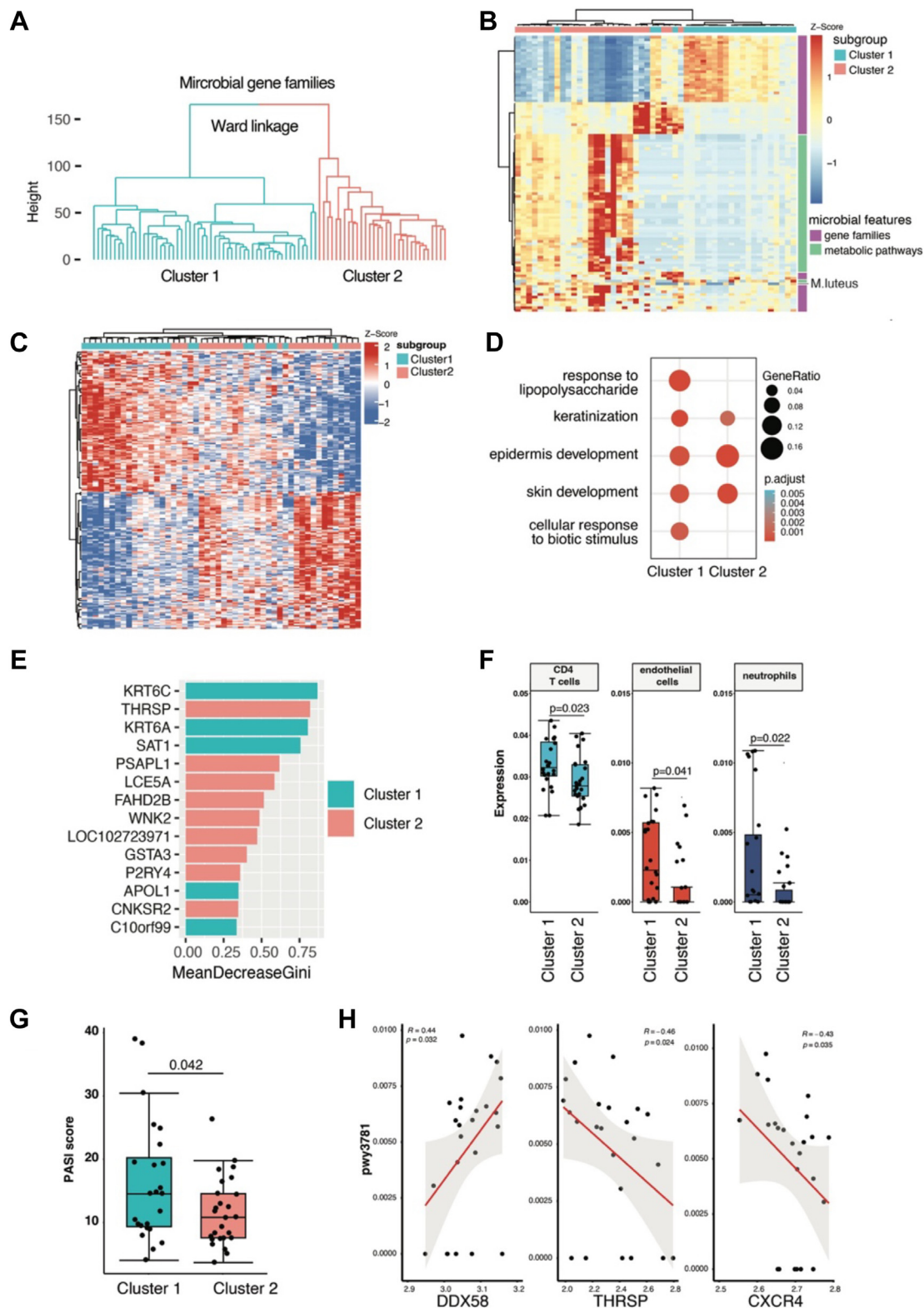


Fig. 6: Psoriasis clusters with distinct microbial metabolic pathways and host genes. (A) The hierarchical dendrogram displays two distinct psoriasis clusters based on microbial gene families. Different colors denote the clusters. Heatmaps summarize microbial functional features

cluster 1 showed overall reduced expression of microbial metabolic pathways, indicating a general scarcity of microbial features in cluster 1. Only aerobic respiration I (PWY-3781, cytochrome c) was highly abundant in cluster 1. The expression of host genes such as *IL36A* and *IL19* were greatly upregulated in cluster 1, suggesting a strong inflammatory response in this cluster (Fig. 6C).

From the functional annotation of host genes, cluster 1 was functionally enriched for pathways in response to lipopolysaccharide and cellular response to biotic stimulus (Fig. 6D). Random forest analysis was conducted to select the most discriminatory host genes between cluster 1 and cluster 2 and plotted in Fig. 6E. CIBERSORT analysis estimated distinct immune cell fractions between the two clusters. Patients in cluster 1 had more abundant CD4 T cells, endothelial cells, and neutrophils than those in cluster 2 (Fig. 6F). These results revealed differential immune responses associated with clusters. Cluster 1 patients had higher T cells and neutrophils counts according to CIBERSORT, suggesting increased disease severity of the disease in cluster 1.

Both the identified microbial features and host gene profiles of cluster 1 and cluster 2 indicated increased disease severity in cluster 1. We used the Wilcoxon test to compare the PASI scores between the two clusters, and cluster 1 exhibited a mildly increased PASI score (Fig. 6G). To further elucidate the underlying mechanisms, we integrated the abundance of microbial metabolic pathway PWY-3781 with host genes. PWY-3781 positively correlated with *DDX58* and negatively correlated with *THRSP* and *CXCR4*, underscoring the importance of this pathway in Pso (Fig. 6H).

The microbial functional features were subsequently regrouped into level 4 enzyme commission (EC) categories to further assess the role of these features in the distinctiveness of the identified Pso clusters. The differential expression analysis revealed that cluster 1 was endowed with diminished expression of EC categories as compared to cluster 2 (Fig. 7A). Only NADH ubiquinone reductase H translocating (EC 7.1.1.2.) (Fig. 7B), Human endogenous retrovirus K endopeptidase (EC 3.4.23.50.) (Fig. 7C), and Ubiquitinyl hydrolase 1 (EC 3.4.19.12.) (Fig. 7D), were highly expressed in cluster 1. To elucidate the interaction between the host and microbes, we then conducted Spearman correlation analysis associating the expression of these three

microbial enzymes with host cutaneous gene expression, as depicted in Fig. 7E.

Discussion

Given the well-established relationship between microbiota and human diseases, numerous studies have focused on elucidating alterations in single-omics layers of psoriatic skin without integrating multiple types of omics data.^{6,7,9,10,52–54} While variations in the microbiome and host genes in psoriatic skin are recognized, interactions between the skin's shotgun microbiome and host genes remain largely uncharted. Our study, for the first time, probes the relationship between host genes and microbial taxonomic and functional features derived from whole metagenomic shotgun sequencing in psoriatic skin, using the extensive and clinically well-characterized MAARS cohort. Our findings spotlight intricate relationship between the host skin transcriptome, the skin microbiome, and the severity of the disease, as well as potentially, novel disease clusters, underlining the heterogeneity of psoriasis, lays the groundwork for understanding host-microbe interactions in psoriasis.

Our results identified a specific WGCNA gene co-expression module, “turquoise”, and gene functional enrichment analysis indicated its correlation with the host immune system and defense responses to viruses. In addition, PPI analysis of the turquoise module revealed that proteins associated with the cell cycle (e.g., CDC20, KIF11), IFN response (e.g., IFI6, IFI27), AMPs (e.g., LCE3A/D/E), and chemokines (e.g., CXCL1, CXCL8) were interconnected, forming distinct sub-networks. Given the strong correlation between turquoise with the Pso lesional group and high PASI score, these findings suggested the role of the overactivation of the host immune system in psoriatic skin and disease severity. It is widely recognized that in psoriatic skin inflammation, there exists a positive feedback loop involving the release of IFN- α . This release, facilitated by the activities of dendritic cells and T cells, triggers hyperkeratosis, local inflammation, and further leukocyte infiltration.⁸ Subsequently, overactivated keratinocytes produce elevated levels of cytokines, AMPs, and chemokines, intensifying keratinocyte proliferation and leukocyte recruitment. The expression of IFN response and AMPs within the module implies their association

(B) and host genes (C) changes within each PSO cluster. Microbial features with more than one count in at least 50% of samples were plotted on the. Features with higher relative abundances are shaded in red, while those with lower relative abundances are shaded in blue. (D) Upregulated host genes within each cluster were further analyzed for functional enrichment using Gene Ontology (GO). (E) Visualization of the host genes, from a comparison between clusters, that exhibited the highest value of mean decrease Gini in the Random Forest (RF) classification. (F) Boxplots illustrate differences in immune cell expression between cluster 1 and cluster 2 by Mann-Whitney U test ($p < 0.05$). Within each boxplot, horizontal lines denote median values; boxes extend from the 25th to the 75th percentile of each group's distribution of values. (G) Boxplot displays variations in the PASI score between cluster 1 and cluster 2, as assessed by Welch's t-test ($p < 0.05$). Within each boxplot, horizontal lines denote median values; boxes extend from the 25th to the 75th percentile of each group's distribution of values. (H) Spearman correlation between the metabolic pathway pwy-3781 and host genes. The grey shadow refers to the 95% confidence interval.

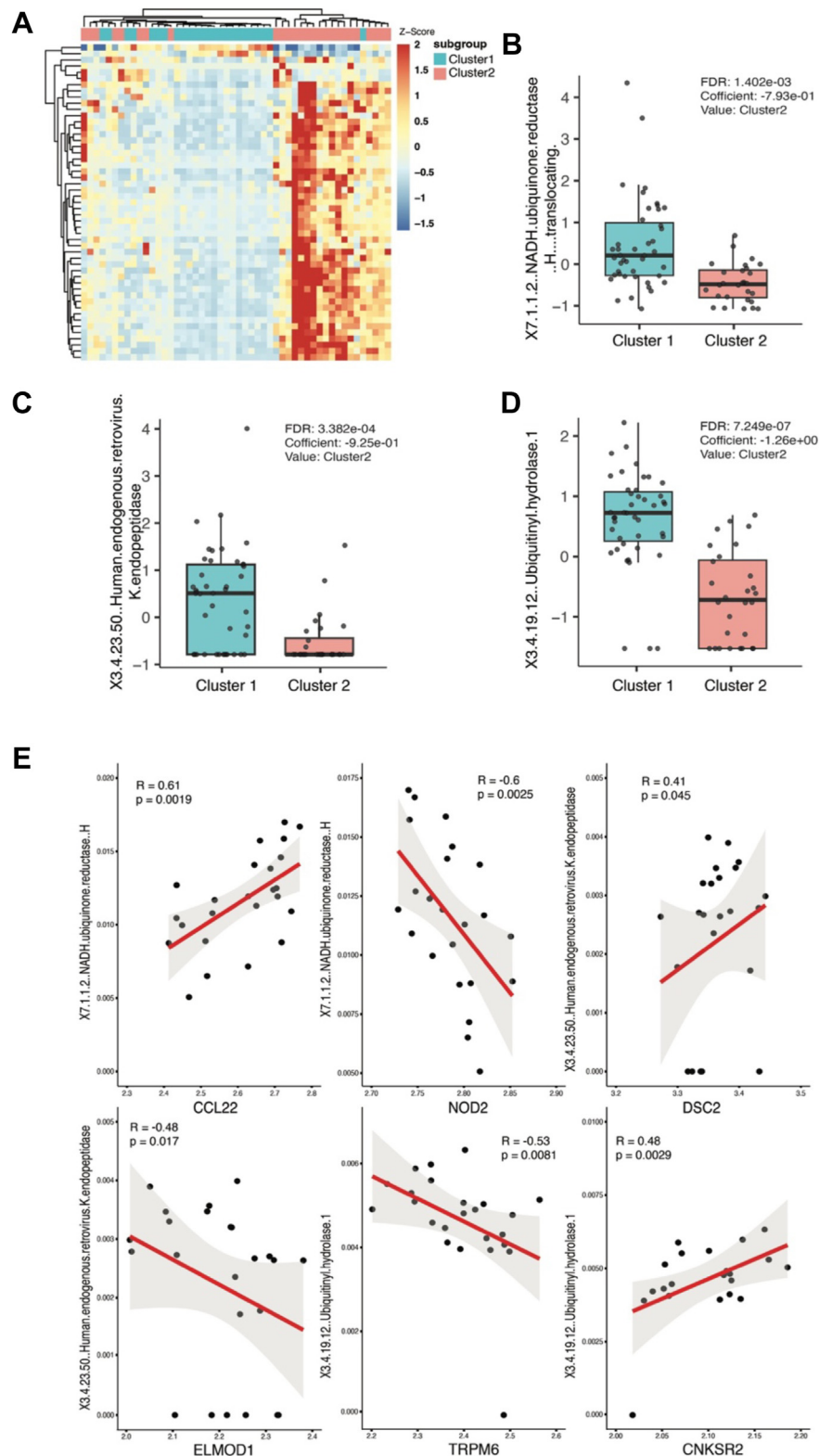


Fig. 7: Psoriasis clusters with distinct enzyme commission categories. (A) Heatmaps summarize the changes in microbial EC categories within each PSO cluster. Microbial features with more than one count in at least 50% of samples were plotted on the. Features with higher

with the severity of psoriasis and their crucial role in potential crosstalk between the host immune system and the skin microbiome.

To further explore the factors related to the severity of Pso, we utilized Spearman correlation analysis to extract host genes associated with disease severity (as represented by PASI scores) lesional and non-lesional psoriatic skin samples, respectively. In line with gene co-expression findings, a disease relevant signature is evident in symptom-free psoriatic skin, and genes from both skin samples were enriched in categories related to virus defense and response. Moreover, our PPI analysis revealed the presence of an IFN response network in both Pso lesional and nonlesional samples. Previous research has pinpointed associations between specific viruses, such as hepatitis C (HEP C), human papillomavirus (HPV), human endogenous retroviruses (HERVs⁵⁵), and the exacerbation or onset of Pso. However, while these earlier studies zoomed in on individual virus species, the role of the entire skin virome in Pso remains an enigma and calls for more comprehensive research.^{55–58} Host genes that correlated with disease severity highlighted an overactive immune system and the enrichment of virus-related functions, reinforcing the possibility of a role for the skin virome in the development or exacerbation of psoriasis. The skin virome variation may critically impact the observed imbalance in the skin microbial community associated with psoriasis. Concurrently, these variations could catalyze the release of IFN, further unsettling the balance of the host immune system, and leading to more severe symptoms.

IFNs, especially Type I IFNs (IFN-I), are crucial for host defense against viral infections, and plasmacytoid dendritic cells (pDCs) have been reported to specialize in the production of IFN-I, making them important mediators of host antiviral responses.^{59,60} The high predicted numbers of keratinocytes, pDCs, and neutrophils identified in lesional psoriatic skin, correlated with the “turquoise” module, may indicate the critical role of viral infection in the severity of psoriasis. Furthermore, it is well-established that through the cGAS-STING pathway, not only foreign microbial DNA but also self-DNA originating from apoptotic processes may trigger type I interferon and NF- κ B signaling.⁶¹ Given that the highly accelerated keratinocyte life cycle and dysregulated maturation may lead to an accumulation of self-DNA in lesions, the possibility that this further sustains inflammatory feedback loops cannot be discarded.

Whole metagenomic shotgun sequencing revealed differences in the microbial communities between the

lesional group and both non-lesional and healthy volunteers, as well as between different PASI levels and healthy volunteers. Notably, *Corynebacterium simulans* occurred at higher abundance in both lesional and nonlesional psoriatic skin. In contrast, there was a lower abundance of *Cutibacterium acnes* in these groups compared with healthy skin. *C. acnes* has been identified as playing a role in maintaining immune system homeostasis by modulating the TH17 cell, while the toxigenic *C. simulans* was hypothesized to be the triggering factor of psoriasis.⁶² Furthermore, our study showed that *C. simulans* occurred at a higher abundance in the PASI-severe and PASI-moderate groups compared to healthy volunteers, and Spearman correlation analysis revealed that the abundance of *C. simulans* was correlated with host genes of turquoise model. More interestingly, many of these host genes are viral sensing related, such as *IFI27*, *IFIT1*, and *DDX60*.⁶³ This suggests a potential interplay between bacteria and viruses in the pathogenesis and severity of psoriasis, emphasizing the importance of integrated studies involving different microbial kingdoms and the longitudinal examination of the bacteria/viruses balance for understanding Pso development. Additionally, our data highlighted correlations between *C. simulans* and *C. acnes* with immune cells and keratinocytes, suggesting the importance of these two bacterial species in psoriasis and indicating the interaction of commensal microorganisms with the host immune system and their potential role in exacerbating Pso.

The functional features of the skin microbiome in the Pso lesional group displayed significant heterogeneity. Based on this observation, we hypothesized the existence of molecular endotypes within the Pso group. Indeed, two distinct Pso clusters, named cluster 1 and cluster 2, were identified through the expression of microbial gene families. Furthermore, cluster 1 had a higher PASI score than cluster 2, which means a more severe condition in patients of cluster 1. After adjusting for confounders, these clusters exhibited distinct expressions of metabolic pathways, enzyme commission categories, and gene families. Cluster 1 predominantly had reduced pathway expression compared to cluster 2, with the exception of pwy-3781 (Aerobic respiration I, cytochrome c). Cluster 2 included elevated *Micrococcus luteus* abundance, inversely related to the PASI score. Moreover, Spearman correlation revealed a relationship between pwy-3781 and host genes, pwy-3781 has been previously reported to be associated with cell apoptosis, the cytochrome c activates pro-caspase 9 via APAF-1 and directs to cell death.^{64,65} Moreover, higher expressions of

relative abundances are shaded in red, while those with lower relative abundances are shaded in blue. Boxplot shows differences in NADH: ubiquinone reductase (H(+)-translocating) (EC 7.1.1.2) (B), Human endogenous retrovirus K endopeptidase (EC 3.4.23.50.) (C), and Ubiquitinyl hydrolase 1 (EC 3.4.19.12.) (D) between cluster 1 and cluster 2. Within each boxplot, horizontal lines denote median values; boxes extend from the 25th to the 75th percentile of each group's distribution of values. (E) Spearman correlation between the EC categories and host genes. The grey shadow refers to the 95% confidence interval.

AMPs and DEFB4A/B were observed in cluster 1, which may induce bacterial death and subsequently lead to the expression of pwy-3781. This, in turn, could trigger an overactivation of the host immune system, contributing to the development of psoriasis in cluster 1. Additionally, a high abundance of CD4 T cells and neutrophils was observed in cluster 1, reinforcing our previous conclusion. The pronounced infiltration of neutrophils, a hallmark of psoriasis, along with respiratory bursts and neutrophil extracellular trap formation, has been associated with psoriasis pathogenesis. The abundance of these immune cells indicates a more aggressive immune response in cluster 1 compared to cluster 2.^{39,66} Correlation results demonstrated interactions between microbes and host genes, emphasizing the importance of microbial functionality. Nevertheless, it remains challenging to pinpoint a single microbial species responsible for these variations, indicating a collective influence of the entire microbial community on Pso development, underscoring the importance of microbial gene functions rather than focusing solely on microbial species.

There are some shortcomings in this study. Our data were limited by a relatively low depth of shotgun sequencing. While we were able to identify the major microbial features in the dataset, we might have overlooked minor variations in these features, preventing further analysis of stratified functional features. Additionally, our dataset is a cross-sectional analysis, and due to the lack of longitudinal data, we cannot investigate changes in microbial and host feature expression and interaction throughout disease development. Moreover, this is an exploratory study, further studies focusing on the mechanisms are needed to deeply and fully understand the factors associated with the severity of Pso. Despite these limitations, our dataset benefits from a relatively large sample size, and all samples were collected from the same location (the lower back), enhancing the reliability of our results and providing specific insights into the interactions between the host and microbes in the skin affected by Psoriasis (Pso).

In conclusion, our multi-omics analysis has, for the first time, revealed the presence of *C. simulans* and antiviral responses associated with disease severity. Additionally, we have identified two psoriatic clusters with distinct AMPs and metabolic pathway expressions. Our data suggest the beneficial role of conducting immunomodulatory and microbiota modulation therapies in parallel and tailoring these therapies for future psoriasis management. Briefly, immunomodulatory management aims to alleviate symptoms and control disease progression, while microbiota modulation seeks to adjust the skin microbiota composition or target the elevated microbes in psoriasis patients to alleviate symptoms. Additionally, personalized management targeting patients from different clusters may yield more effective outcomes. Overall, our results provide novel insights into the association between host gene

expression and the skin microbiome in psoriasis and pave the way for tailored therapies for psoriasis patients.

Contributors

Conceptualization: YY, HA; Visualization: YY, HA; Data analysis: YY, HA; Resources: BH, AL, JB, BA, HA; Writing—Original Draft: YY, HA; Writing—Review & Editing: YY, PO, ZR, GM, AS, VS, JB, AL, BA, BH, NF, HA; Project Administration: YY, HA; Verified underlying data: YY, HA. All authors read and approved the final version of the manuscript.

Data sharing statement

MAARS metagenomics and transcriptomic data are available in the Sequence Read Archive (SRA) under accession PRJNA1000281 and EBI Array Express under accession E-MTAB-8149 respectively.

The public reference databases used in this study are as follows: GRCh38 (https://genome-id3.s3.amazonaws.com/bt/GRCh38_noalt_as.zip), Metacyc database (<https://metacyc.org/>), DerM22 database (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6698047/>), The LM22 database (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5895181/>).

All other relevant data are available from the authors.

Declaration of interests

Prof. Homey declared a conflict of interests as described in the ICMJE DISCLOSURE FORM. All the other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.ebiom.2024.105222>.

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