Clinical, Cosmetic and Investigational Dermatology

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Integrative Analysis of Arachidonic Acid Metabolism in the Pathogenesis and Immune Dysregulation of Psoriasis

Mengyi Hou[1], Yanting Sun[2]

[1]Department of Laboratory Medicine, People's Hospital of Chongqing Liang Jiang New Area, Chongqing, 401122, People's Republic of China; [2]Centre of Clinical Laboratory, The First Affiliated Hospital of Soochow University, Suzhou, 215006, People's Republic of China

Correspondence: Yanting Sun, Centre of Clinical Laboratory, The First Affiliated Hospital of Soochow University, Suzhou, 215006, People's Republic of China, Email 397104986@qq.com

Background: Psoriasis is a chronic inflammatory skin disorder with complex molecular mechanisms. While previous studies have demonstrated altered levels of arachidonic acid and its metabolites in psoriatic lesions, the specific roles of arachidonic acid metabolism (AAM) genes in the molecular pathogenesis and immune dysregulation of psoriasis remain poorly understood. This study aimed to investigate the role of AAM genes in the pathogenesis and immune dysregulation of psoriasis using an integrative bioinformatics approach.

Methods: Gene expression data from psoriasis patients and healthy controls were obtained from the Gene Expression Omnibus database and analyzed. Differentially expressed genes were identified, and functional enrichment analyses were performed. Weighted gene co-expression network analysis (WGCNA) and machine learning techniques were employed to identify psoriasis associated AAM genes. Single-sample gene set enrichment analysis (ssGSEA) and immune cell composition analysis were conducted to explore functional implications. Transcription factor prediction analysis was performed to identify potential regulators of key AAM genes.

Results: Differential expression analysis revealed 469 dysregulated genes in psoriasis, with functional enrichment highlighting the involvement of epidermis development, immune response, and inflammation. WGCNA and machine learning approaches identified *ABCC1, PLA2G3, CYP2J2*, and *GPX2* as key AAM genes. ssGSEA showed elevated inflammation and immune response in psoriasis, with key AAM genes correlating with specific pathways. Immune cell composition analysis revealed increased infiltration of inflammatory cells in psoriatic skin. Transcription factor prediction analysis identified shared transcription factors for the key AAM genes, suggesting coordinated regulation of their expression in psoriasis.

Conclusion: This integrative analysis identified key AAM genes associated with psoriasis pathogenesis and immune dysregulation, providing novel insights into the molecular basis of psoriasis. The findings highlight potential therapeutic targets and biomarkers, which could lead to improved diagnosis and treatment strategies for this chronic inflammatory skin disorder.

Keywords: psoriasis, arachidonic acid metabolism, immune dysregulation, integrative analysis

Introduction

Psoriasis is a common, chronic inflammatory skin disorder affecting approximately 0.14–1.99% of the world population, with variations across different regions.[1] Psoriasis manifests in various clinical symptoms, including plaque, guttate, erythrodermic, and pustular forms, each with distinct morphological features and distribution patterns.[2,3] Psoriasis significantly impacts the quality of life of suffering patients, often leading to depression, anxiety, and increased risk of suicidality.[4] The severity of psoriasis ranges from mild to severe, and the condition is frequently associated with multiple comorbidities, such as psoriatic arthritis, metabolic syndrome, and cardiovascular disease, further contributing to the overall disease burden.[2] Current treatment strategies encompass topical therapies, phototherapy, conventional systemic agents, and biologic drugs targeting key inflammatory pathways, such as TNF-α, IL-23, and IL-17.[2,3] Although the exact

Received: 5 September 2024
Accepted: 28 February 2025
Published: 17 March 2025

etiology of psoriasis remains elusive, growing evidence suggests that dysregulation of immune pathways and metabolic processes play crucial roles in its pathogenesis.[5]

Arachidonic acid, a polyunsaturated omega-6 fatty acid, is a crucial component of cell membranes and serves as a precursor for various bioactive lipid mediators.[6] Arachidonic acid is metabolized through three main enzymatic pathways: the cyclooxygenase, lipoxygenase, and cytochrome P450 pathways, which produce eicosanoids such as prostaglandins, leukotrienes, and epoxyeicosatrienoic acids (EETs), respectively.[6] Dysregulation of arachidonic acid metabolism (AAM) has been implicated in the pathogenesis of several immune and inflammatory diseases, including inflammatory bowel disease, kidney inflammation, and asthma.[7–9] While previous studies have demonstrated altered levels of arachidonic acid and its metabolites in psoriatic lesions, suggesting AAM in the pathogenesis of psoriasis,[10–13] the specific roles of AAM genes in the molecular pathogenesis and immune dysregulation of psoriasis remain poorly understood.

In this study, we employed an integrative bioinformatics approach to investigate the dysregulation of AAM in psoriasis. We performed differential expression analysis to identify differentially expressed genes (DEGs) and elucidate the biological processes and pathways involved in psoriasis pathogenesis. Weighted gene co-expression network analysis (WGCNA) was conducted to identify psoriasis-associated co-expression modules, which were then integrated with known AAM genes. Machine learning techniques were employed to identify key AAM genes. Furthermore, we investigated the functional implications of these genes using pathway enrichment and immune cell infiltration analyses. Finally, transcription factor prediction analysis was performed to uncover potential regulators of key AAM genes. Our findings aim to provide a comprehensive understanding of the role of AAM in psoriasis pathogenesis and immune dysregulation, potentially facilitating the development of novel diagnostic and therapeutic strategies for this chronic inflammatory skin disorder.

Methods

Data Acquisition and Preprocessing

Gene expression matrices for the GSE13355,[14] GSE78097,[15] and GSE14905[16] datasets were obtained from the Gene Expression Omnibus (GEO) database. These datasets were selected based on the following inclusion criteria: (1) inclusion of both psoriasis and healthy control samples, (2) derivation from skin tissue, and (3) availability of raw gene expression data. The GSE13355 dataset (annotation file GPL570) included expression profiles of 64 patients, with 58 controls used for analysis. The GSE78097 (annotation file GPL13534) and GSE14905 (annotation file GPL570) datasets were used for expression validation, comprising 27 patients and 6 controls, and 33 patients and 21 controls, respectively. Each dataset was analyzed independently to avoid potential confounding factors between different experimental platforms. The raw gene expression data were preprocessed by log2 transforming if necessary, and removing batch effects using the normalizeBetweenArrays function from the limma package.[17] A total of 101 genes related to AAM were obtained from the Gene Ontology term "ARACHIDONIC_ACID_METABOLIC_PROCESS", the Reactome pathway "REACTOME_ARACHIDONIC_ACID_METABOLISM", and the KEGG pathway "ARACHIDONIC_ACID_METABOLISM".

Identification of Differentially Expressed Genes

Differential expression analysis of the GSE13355 dataset was conducted using the limma package[17] to compare the psoriasis group to the control group. Genes with an absolute log2 fold change greater than 1 and an adjusted p-value less than 0.05 were considered significantly differentially expressed. Heatmap and volcano plot visualizations were generated using the pheatmap[18] and gglot2[19] packages, respectively.

Functional Enrichment Analysis

To identify significantly enriched Gene Ontology (GO) terms and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways associated with the DEGs, enrichment analyses were performed using the clusterProfiler package.[20] The top 8 enriched GO terms and the top 20 KEGG pathways were visualized using bar plots.

Gene Set Enrichment Analysis (GSEA)

GSEA was conducted using the clusterProfiler package[20] to identify significantly enriched pathways in the psoriasis group compared to the control group. The pre-ranked gene list, based on their log2 fold change values, was used as input along with the gene set information obtained from the MSigDB Hallmark gene sets and KEGG pathway database.

WGCNA

WGCNA was performed using the WGCNA package[21] to identify gene modules associated with psoriasis. Genes with high variability (top 25% most variable genes based on standard deviation) were selected for further analysis. Sample clustering was performed to detect outliers (cutHeight=20000). A soft-thresholding power value of 10 was used for constructing the weighted gene co-expression network. The minimum module size was set to 100, and modules were identified using dynamic tree cutting with a deepSplit value of 2. Module-trait relationships were assessed through correlation analysis with disease status (Control vs Psoriasis). Among the identified modules, we focused on the module showing the strongest positive correlation with disease status, and examined its intersection with genes involved in AAM.

Machine Learning Analysis

Lasso regression was performed using the glmnet package,[22] with binomial family specification for the logistic model. The analysis included 10-fold cross-validation to determine the optimal lambda value that minimized deviance. Genes with non-zero coefficients at the minimum lambda value were extracted as the Lasso signature genes, excluding the intercept term. Support Vector Machine Recursive Feature Elimination (SVM-RFE) was conducted using the e1071 package,[23] with 10-fold cross-validation applied to the combined gene expression and sample group data. The algorithm performed recursive feature elimination by halving features above 50. Feature genes were selected based on the minimum validation error, which was determined through an iterative feature sweep of the top 25 ranked features. The optimal number of feature genes was determined by the position of minimum error in the validation curve, and these genes were extracted as the final SVM-RFE signature. Random forest analysis was carried out using the randomForest package,[24] with an initial model trained using 500 trees. The optimal number of trees was determined by identifying the point with the minimum error rate, and a second random forest model was then trained using this optimal number of trees. The top 10 genes were selected based on their importance scores as measured by the Mean Decrease Gini index. Genes with the top 10 importance scores were selected as key features. The Venn diagram was generated to identify overlapping genes among the three machine learning methods.

Single-Sample Gene Set Enrichment Analysis (ssGSEA)

ssGSEA was conducted using the GSVA package[25] to assess the enrichment of the Hallmark gene sets in each sample of the psoriasis group. The gene expression matrix was preprocessed and normalized, and the ssGSEA scores were calculated using the gsva function. Differential enrichment of gene sets between the control and psoriasis groups was visualized using boxplots. Correlation analysis was performed between the ssGSEA scores and the expression levels of key AAM genes in the psoriasis group using Spearman correlation test.

Immune Cell Composition Analysis

Immune cell composition analysis was performed using the CIBERSORT method with the LM22 signature matrix.[26] Differences in immune cell fractions between the control and psoriasis groups were visualized with boxplots using the ggplot2 package.[19] Correlation analysis between gene expression and immune cell composition in the psoriasis group was conducted using Spearman correlation test and visualized with a heatmap.

Transcription Factor Prediction Analysis

To predict potential transcription factors regulating the expression of key AAM genes, we performed transcription factor target gene enrichment analysis for key AAM genes using the NetworkAnalyst online tool (https://www.networkanalyst.

ca/NetworkAnalyst/). This tool integrates the JASPAR transcription factor binding site profile database to infer transcription factor-gene interactions.

Statistical Analysis

Statistical analyses were performed using R (version 4.3.1). For comparisons between psoriasis and control groups, the Wilcoxon rank-sum test was used for continuous variables. Correlation analyses were conducted using Spearman's rank correlation test. p-values < 0.05 were considered statistically significant.

Results

Identification of DEGs

To identify genes that are significantly dysregulated in psoriasis, we performed differential expression analysis comparing psoriatic lesional skin samples to normal skin samples using the GSE13355 dataset. The volcano plot (Figure 1A) displays the distribution of DEGs, where we identified 469 DEGs (|log2 fold change| > 1, adjusted p-value < 0.05), with 284 genes being upregulated and 185 genes being downregulated in psoriasis. To better visualize the expression patterns of the most significantly dysregulated genes, we generated a heatmap (Figure 1B) displaying the relative expression levels of the top 30 upregulated and top 30 downregulated genes. The expression values were normalized using z-score row scaling, and genes were hierarchically clustered based on their expression similarity.

Functional Enrichment Analysis

To elucidate the biological processes and pathways involved in psoriasis, we conducted functional enrichment analysis on the DEGs. GO analysis revealed significant enrichment of terms related to epidermis development, keratinocyte differentiation, and response to lipopolysaccharide (biological process), secretory granule lumen and collagen-containing extracellular matrix (cellular component), and serine-type endopeptidase activity and cytokine receptor binding (molecular function) (Figure 2A). KEGG pathway analysis highlighted the involvement of immune response and inflammation pathways, such as cytokine-cytokine receptor interaction, IL-17 signaling, viral infections, and chemokine signaling, as well as the AAM pathway (Figure 2B).

To further investigate the dysregulated pathways in psoriasis, we performed GSEA on the GSE13355 dataset. The results revealed several upregulated pathways, including E2F targets, the G2M checkpoint, and interferon alpha and

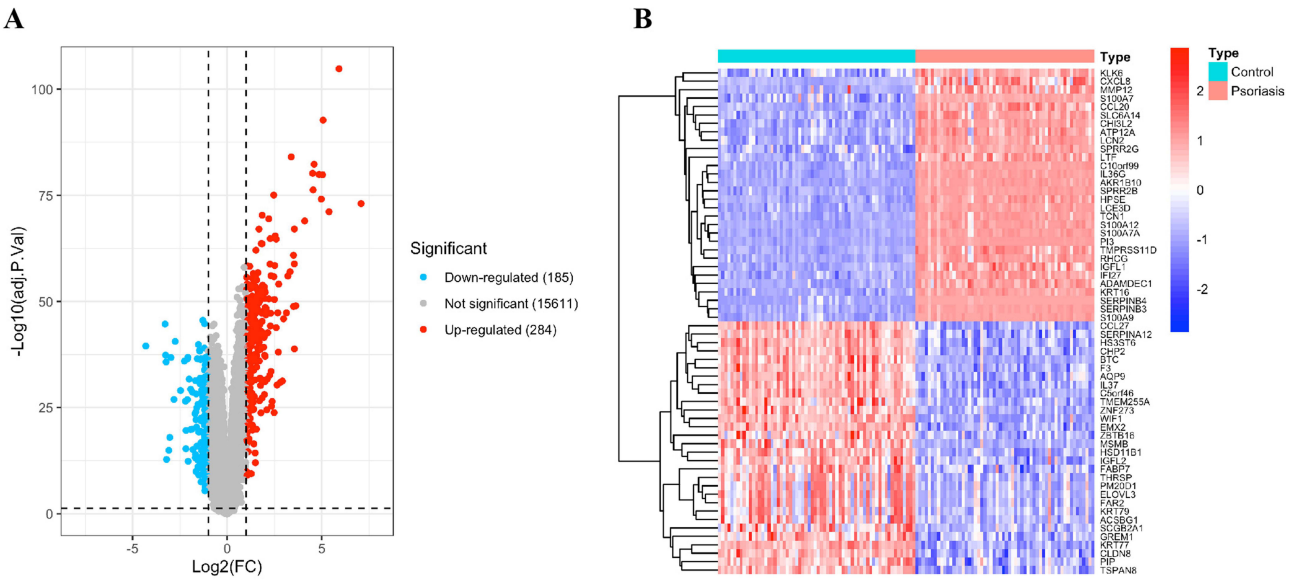

Figure 1 Differentially expressed genes (DEGs) analysis. (**A**) Volcano plot depicting DEGs between psoriasis and control samples from the GSE13355 dataset. The x-axis shows the log2 fold change (FC), and the y-axis represents the -log10 of the adjusted p-value. (**B**) Heatmap visualization of the top 30 upregulated and top 30 downregulated genes in psoriatic lesions compared to normal skin samples from the GSE13355 dataset.

 https://doi.org/10.2147/CCID.S494806

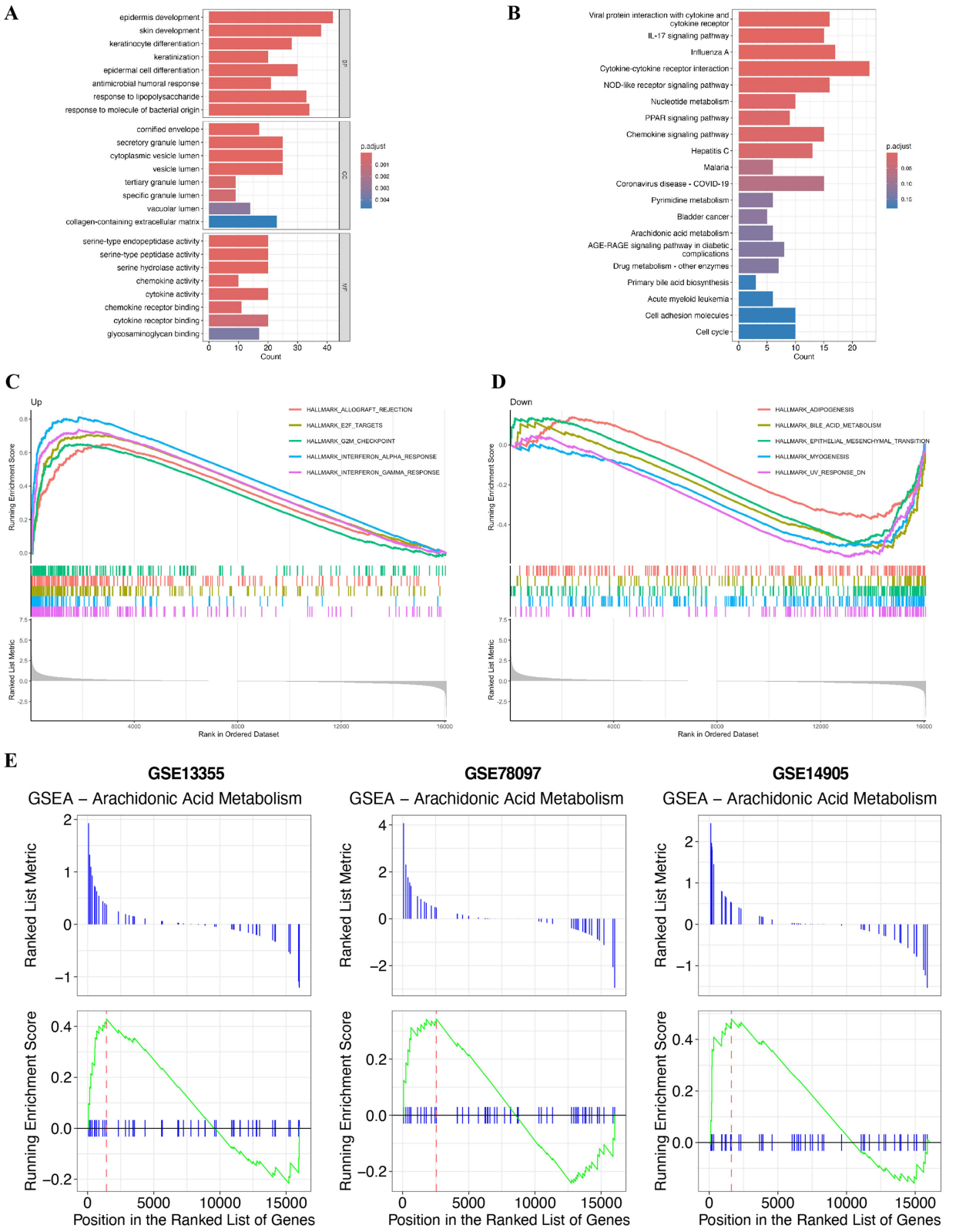

Figure 2 Functional enrichment analysis in psoriasis. (**A**) The bar plot displays the top 8 significantly enriched Gene Ontology (GO) terms in each category (biological process, cellular component, and molecular function). (**B**) The bar plot shows the top 20 significantly enriched Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways. (**C**) Gene Set Enrichment Analysis (GSEA) plot illustrating the top 5 positively enriched hallmark pathways in psoriasis samples compared to control samples. (**D**) GSEA plot displaying the top 5 negatively enriched hallmark pathways in psoriasis samples compared to control samples. (**E**) GSEA plots demonstrating the consistent upregulation of the arachidonic acid metabolism (AAM) pathway in psoriatic lesions across three independent datasets (GSE13355, GSE78097, and GSE14905).

https://doi.org/10.2147/CCID.S494806

gamma responses (Figure 2C), while several pathways that were significantly downregulated in psoriasis included adipogenesis, bile acid metabolism, and epithelial-mesenchymal transition (Figure 2D). To further validate the involvement of the AAM pathway in psoriasis, we performed GSEA on the GSE13355 dataset and two additional independent datasets (GSE78097 and GSE14905). Consistently, we found significant upregulation of the AAM pathway in psoriatic samples across all three datasets (Figure 2E). These findings suggest the involvement of skin-specific processes, immune response, extracellular matrix remodeling, and metabolic alterations in psoriasis pathogenesis.

Identification of Psoriasis-Associated Co-Expressed Gene Modules

To identify co-expressed gene modules associated with psoriasis, we first selected the top 25% most variant genes based on their standard deviation across samples. These genes were then used as input for the WGCNA analysis on the GSE13355 dataset. The optimal soft-thresholding power of 10 was selected to ensure a scale-free network topology (Figure 3A). Four modules were obtained using the dynamic tree method (Figure 3B and C), with the turquoise module exhibiting a strong positive correlation with psoriasis (Figure 3D).

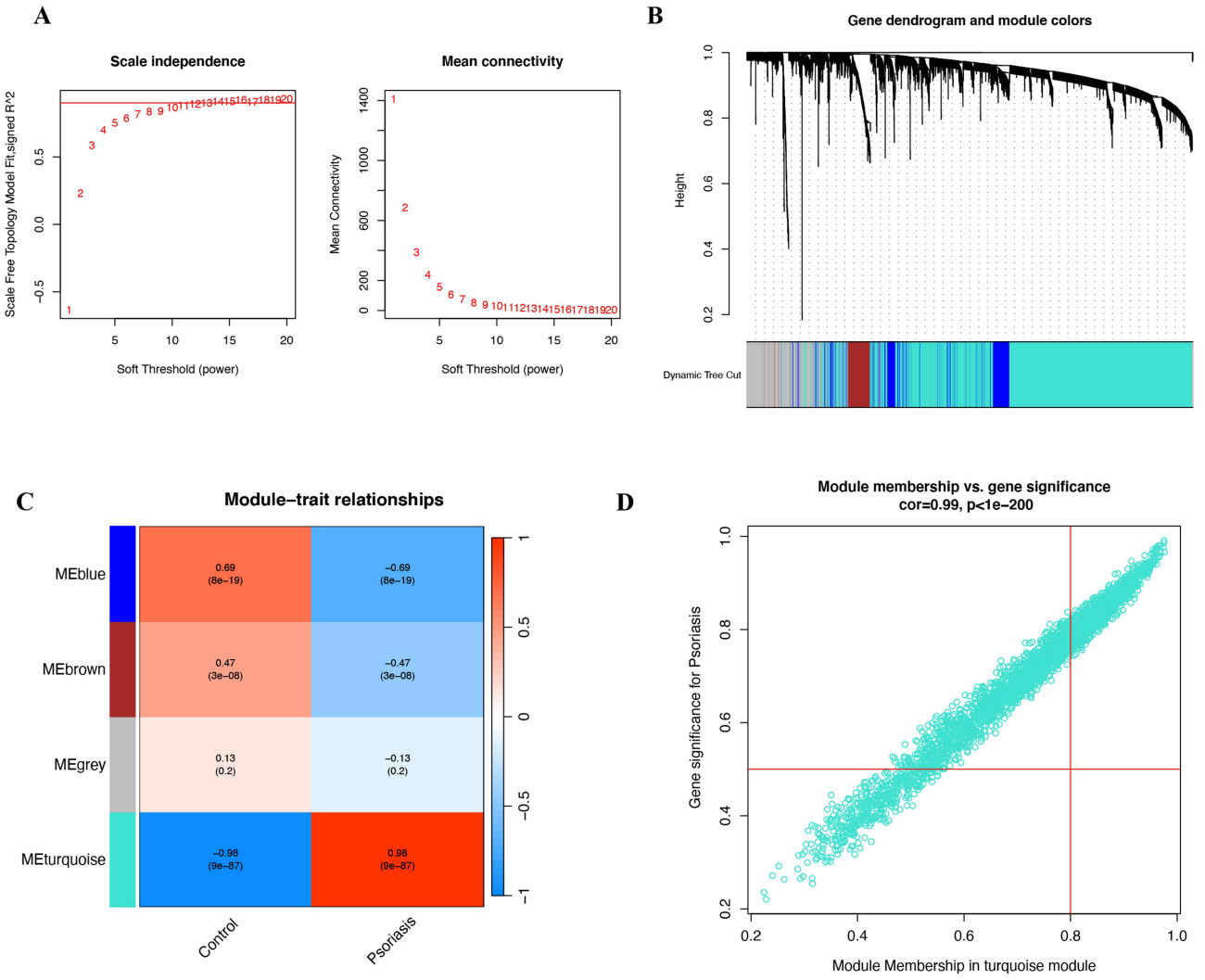

Figure 3 Identification of co-expressed gene modules associated with psoriasis using weighted gene co-expression network analysis (WGCNA). (**A**) Determination of the soft-thresholding power for the construction of a scale-free network. A soft-thresholding power of 10 was selected. (**B**) Gene dendrogram and corresponding module colors obtained through hierarchical clustering of genes based on their topological overlap dissimilarity measure. (**C**) Heatmap representing the correlations between gene modules and sample traits (control and psoriasis) based on the module eigengenes (MEs). The numbers in the cells represent the correlation values and the corresponding p-values for each correlation. (**D**) Scatter plot illustrating the relationship between gene significance (GS) for psoriasis and module membership (MM) within the turquoise module. The plot demonstrates a strong positive correlation between GS and MM.

 https://doi.org/10.2147/CCID.S494806

Identification and Functional Analysis of Psoriasis-Associated AAM Genes

Given the consistent upregulation of the AAM pathway in psoriasis, we sought to identify specific AAM genes associated with the disease. We integrated the 101 AAM genes obtained from relevant databases (see Methods) with the co-expression modules identified by WGCNA, revealing 25 overlapping genes as psoriasis-associated AAM genes (Figure 4A). To validate the expression patterns of these identified genes, we analyzed three independent datasets (GSE13355, GSE14905, and GSE78097). Notably, several AAM genes, including *ABCC1, PLA2G3*, and *GPX2*, exhibited consistent upregulation in psoriatic samples compared to controls across all three datasets. In contrast, genes such as *CYP2J2* were found to be significantly downregulated in psoriatic lesions (Figure 4B–D). Pathway enrichment analysis of psoriasis-associated AAM genes revealed significant enrichment not only in AAM but also in chemical carcinogenesis - DNA adducts, linoleic acid metabolism, metabolism of xenobiotics by cytochrome P450, and serotonergic synapse pathways (Figure 4E).

Identification of Key AAM Genes in Psoriasis

To identify a key set of AAM genes associated with psoriasis, we employed various machine learning techniques. Lasso regression analysis was used to determine the optimal lambda value for feature selection, resulting in 13 key genes (Figure 5A and B). SVM analysis with 10-fold cross-validation demonstrated the highest accuracy and lowest error when using the 4 selected features (Figure 5C and D). Random forest analysis further validated the top 10 most important AAM genes (Figure 5E). Notably, the Venn diagram analysis revealed that four genes—*ABCC1, PLA2G3, CYP2J2*, and *GPX2*—were consistently identified as important across all three machine learning models (Figure 5F).

Functional Implications of Key AAM Genes in Psoriasis

ssGSEA was performed to explore the functional implications of the key AAM genes in psoriasis. The analysis revealed that psoriasis samples exhibited elevated activity in pathways related to inflammation and immune response, while pathways associated with cholesterol homeostasis, androgen response, epithelial-mesenchymal transition, fatty acid metabolism, and UV response (down) were significantly less active compared to controls (Figure 6A).

Correlation analysis unveiled significant associations between the expression of key AAM genes and hallmark pathway activities in psoriasis samples (Figure 6B). *PLA2G3* expression showed positive correlations with mTORC1 signaling, MYC targets, p53 pathway, and PI3K/AKT/mTOR signaling. *GPX2* expression was positively correlated with cholesterol homeostasis and interferon alpha and gamma responses, as well as KRAS signaling (down). *CYP2J2* expression exhibited positive correlations with KRAS signaling (down) and negative correlations with angiogenesis, coagulation, complement, epithelial-mesenchymal transition, and KRAS signaling (up). Lastly, *ABCC1* expression was positively correlated with estrogen response, glycolysis, hypoxia, MYC targets, and p53 pathway.

Immune Cell Composition Analysis

Analysis of immune cell infiltration in control and psoriasis skin samples revealed significant differences in the fractions of several immune cell types. Psoriasis samples exhibited a markedly higher fraction of $CD8^+$ T cells, activated CD4 memory T cells, follicular helper T cells, M1 macrophages, activated dendritic cells, activated mast cells, and neutrophils compared to control samples, but lower fractions of regulatory T cells and resting mast cells (Figure 7A). *PLA2G3* expression showed a positive correlation with activated mast cells, M0 macrophages, and activated dendritic cells, and a negative correlation with M2 macrophages and monocytes (Figure 7B). *GPX2* expression negatively correlated with resting mast cells and dendritic cells (Figure 7B). Similarly, *CYP2J2* expression negatively correlated with resting mast cells and M2 macrophages (Figure 7B). Lastly, *ABCC1* expression was positively correlated with activated mast cells, neutrophils, and activated dendritic cells, but negatively correlated with memory B cells, resting mast cells, and gamma delta T cells (Figure 7B).

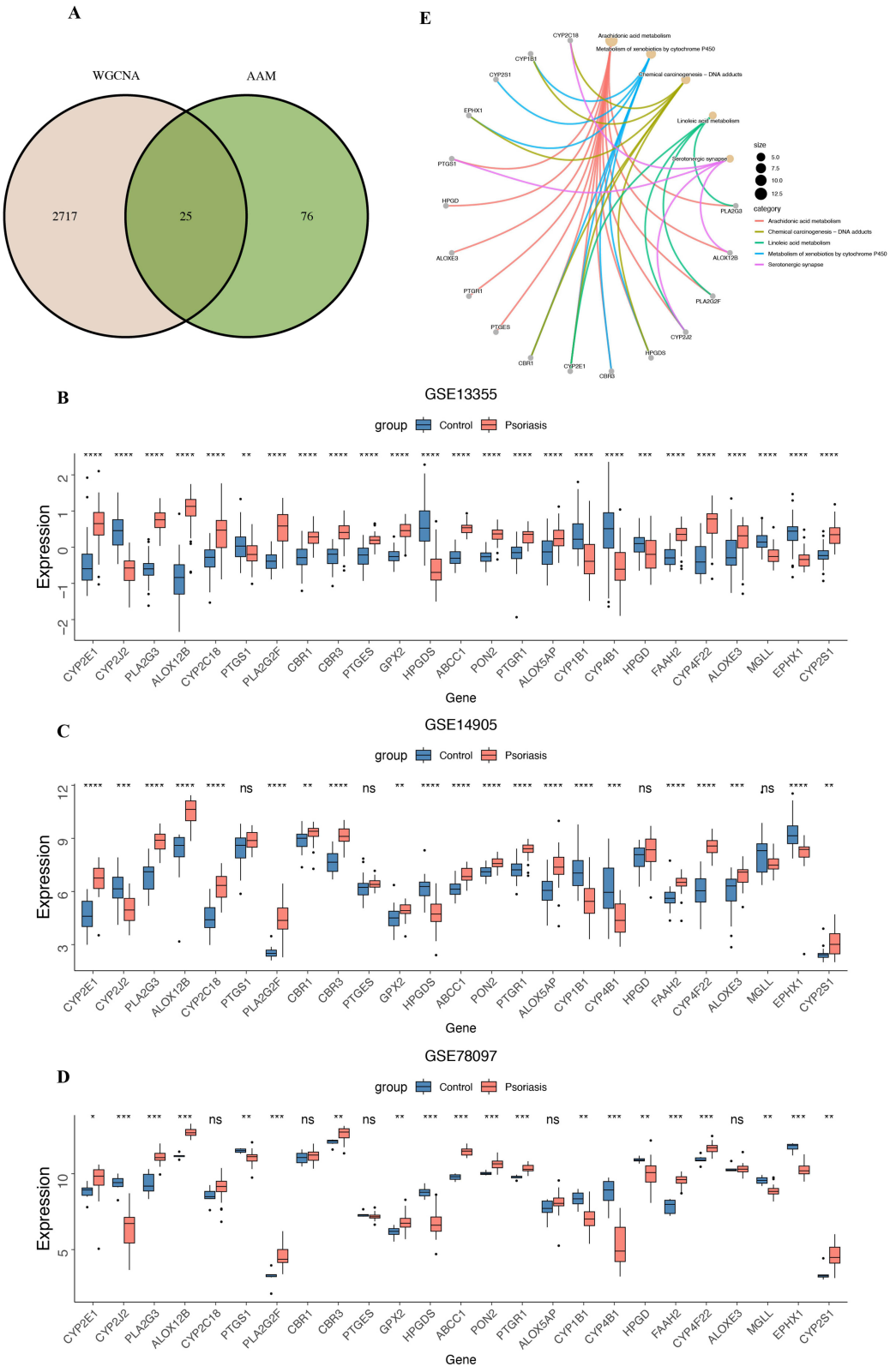

Figure 4 Analysis of psoriasis-associated AAM genes. (**A**) Venn diagram depicting the overlap between the 101 AAM genes obtained from relevant databases and the genes assigned to the psoriasis-associated turquoise module identified through WGCNA analysis. (**B**–**D**) Expression levels of psoriasis associated AAM genes in control and psoriasis patients from three independent datasets: GSE13355 (**B**), GSE14905 (**C**), and GSE78097 (**D**). Statistical significance was assessed using the Wilcoxon rank-sum test (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$). (**E**) KEGG pathway enrichment analysis of the 25 psoriasis-associated AAM genes.

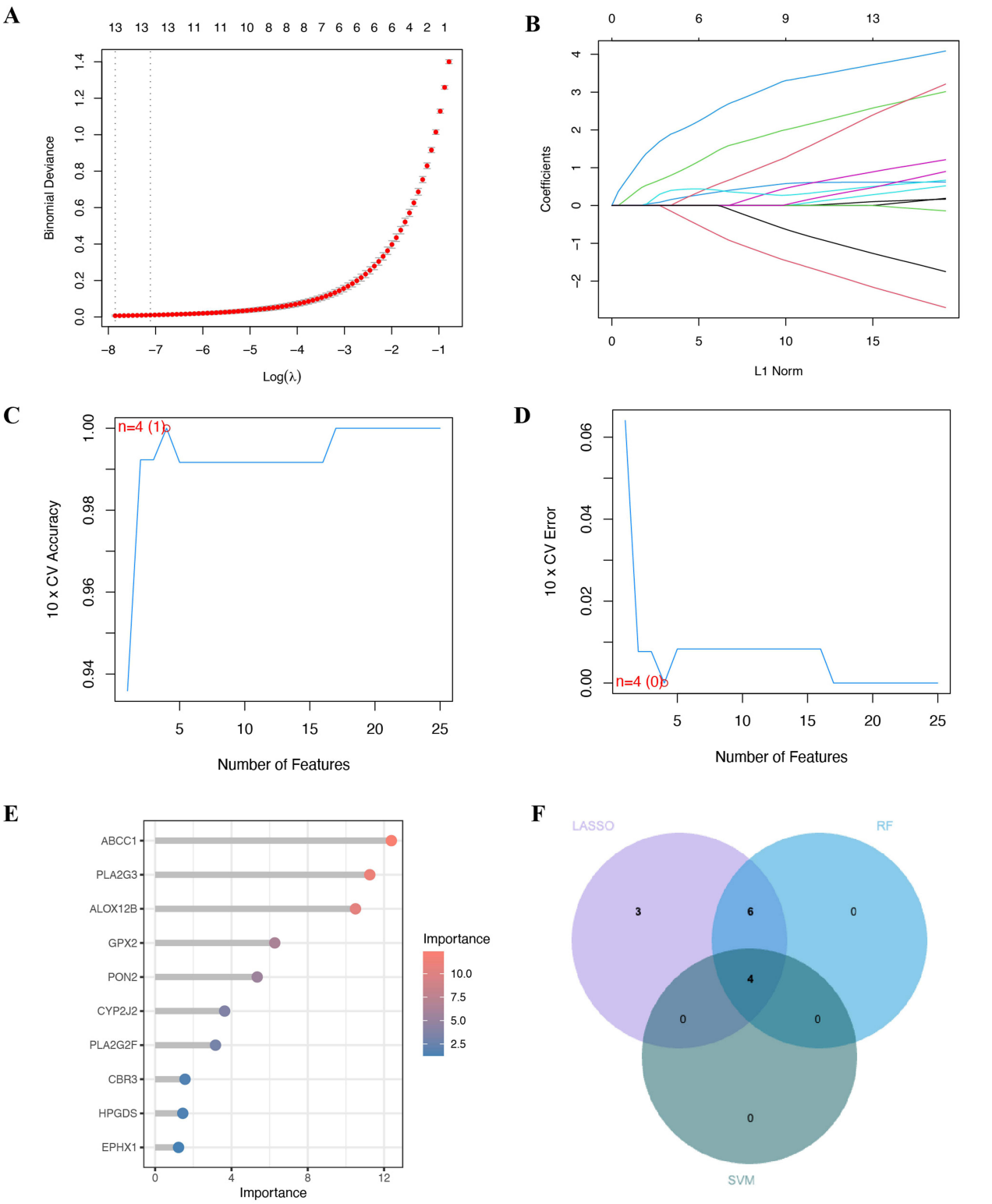

Figure 5 Identification of psoriasis associated key AAM genes using machine learning approaches. (**A**) Partial likelihood deviance plot of Lasso logistic regression. The optimal lambda value is selected based on the minimum cross-validated deviance. (**B**) Lasso coefficient profiles for the genes across the 10-fold cross-validation process. Genes with non-zero coefficients at the optimal lambda value were selected as the Lasso signature genes. (**C**) The accuracy curve for 10-fold cross-validation of the Support Vector Machine Recursive Feature Elimination (SVM-RFE) method, showing the iterative feature sweep of the top 25 ranked features. The optimal number of feature genes is determined based on the minimum validation error. (**D**) The error rate curve for 10-fold cross-validation of the SVM-RFE method. (**E**) Feature importance plot from the Random Forest (RF) model, highlighting the top 10 important genes based on the Mean Decrease Gini index. (**F**) Venn diagram illustrating the overlap of important features identified by SVM-RFE, RF, and Lasso models.

https://doi.org/10.2147/CCID.S494806

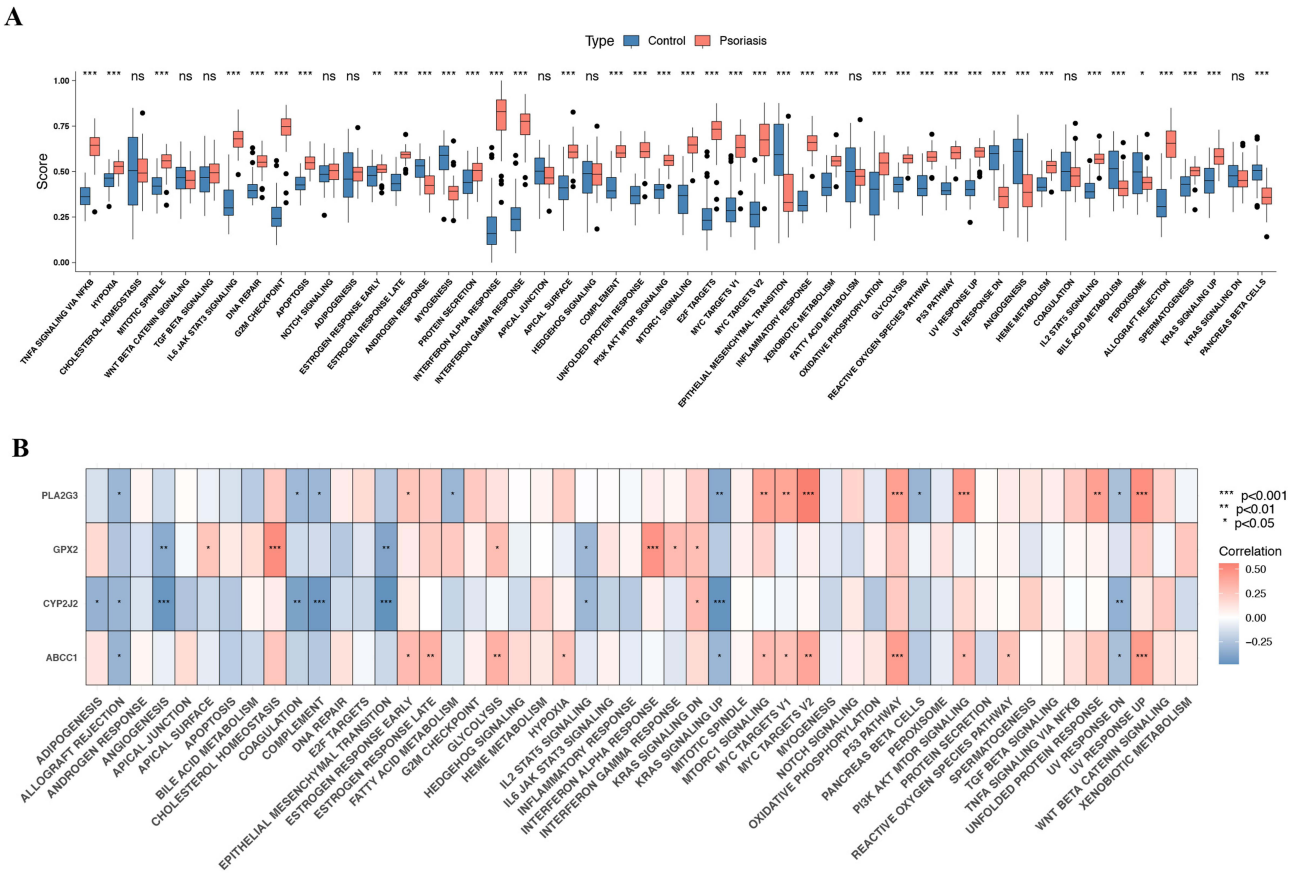

Figure 6 Single-sample gene set enrichment analysis (ssGSEA) of key AAM genes. (**A**) ssGSEA scores of hallmark pathways in control and psoriasis samples from the GSE13355 dataset. Statistical significance was assessed using the Wilcoxon rank-sum test (*p < 0.05, **p < 0.01, ***p < 0.001). (**B**) Correlation heatmap depicting the Spearman's rank correlation coefficients between the expression levels of key AAM genes and the ssGSEA scores of hallmark pathways in psoriasis samples from the GSE13355 dataset. Asterisks denote the statistical significance of the correlations (*p < 0.05, **p < 0.01, ***p < 0.001).

Transcription Factor Prediction Analysis of Key AAM Genes

To further investigate the potential transcription factors regulating the expression of key AAM genes, we performed transcription factor prediction analysis for *ABCC1, PLA2G3, CYP2J2*, and *GPX2* (Figure 8). The results revealed that *ABCC1* and *GPX2* share several common regulatory transcription factors, including HNF4A, HOXA5, NFIC, FOXC1, and JUN. This suggests that these transcription factors may play important roles in the pathogenesis of psoriasis by coordinately regulating the expression of *ABCC1* and *GPX2*. Interestingly, *PLA2G3, CYP2J2*, and *GPX2* were predicted to be commonly enriched for the transcription factor GATA2, indicating that GATA2 may be a key transcription factor regulating the expression of multiple AAM genes. These findings provide new clues and directions for further investigating the role of AAM genes in the development of psoriasis.

Discussion

In this study, we investigated the role of AAM genes in the pathogenesis and immune dysregulation of psoriasis by analyzing transcriptomic data from psoriasis patients and healthy controls. We identified key differentially expressed AAM genes, including *ABCC1, PLA2G3, CYP2J2*, and *GPX2*, and demonstrated their association with specific cellular processes, signaling pathways, and immune cell types in psoriatic lesions. Transcription factor analysis revealed shared regulatory factors for these key genes, suggesting coordinated regulation of their expression in psoriasis. Our findings provide novel insights into the complex molecular mechanisms underlying psoriasis, highlighting potential therapeutic targets, biomarkers, and regulatory mechanisms. This study lays the foundation for developing improved diagnostic and treatment strategies for this chronic inflammatory skin disorder.

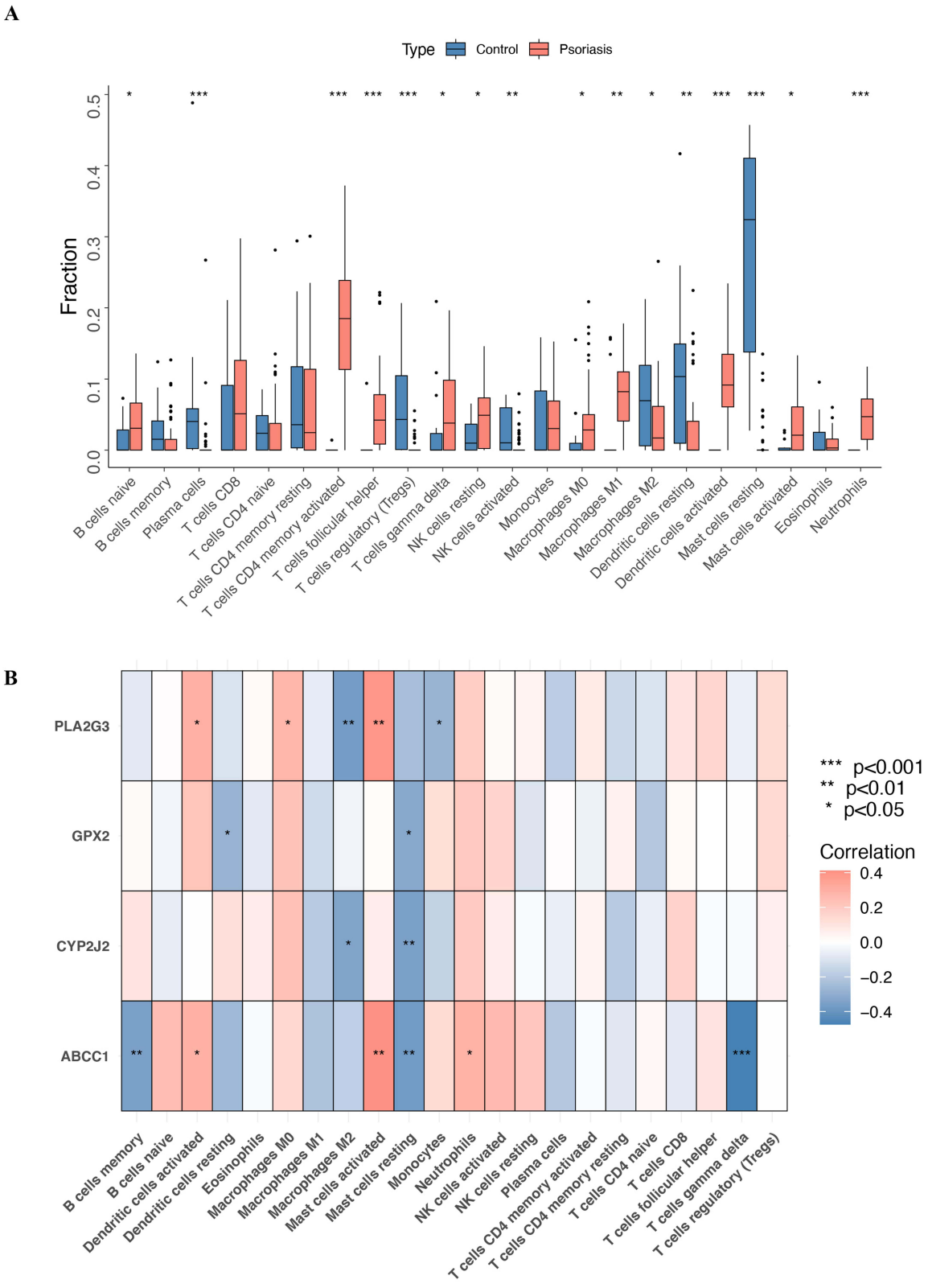

Figure 7 Immune cell infiltration analysis in psoriasis. (**A**) Fractions of various immune cell types in control and psoriasis groups from the GSE13355 dataset, estimated using the CIBERSORT algorithm with the LM22 signature matrix. Statistical significance was assessed using the Wilcoxon rank-sum test (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$). (**B**) Correlation heatmap illustrating the Spearman's rank correlation coefficients between the expression levels of key AAM genes and the fractions of immune cell types in psoriasis samples from the GSE13355 dataset. Asterisks denote the statistical significance of the correlations (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$).

https://doi.org/10.2147/CCID.S494806

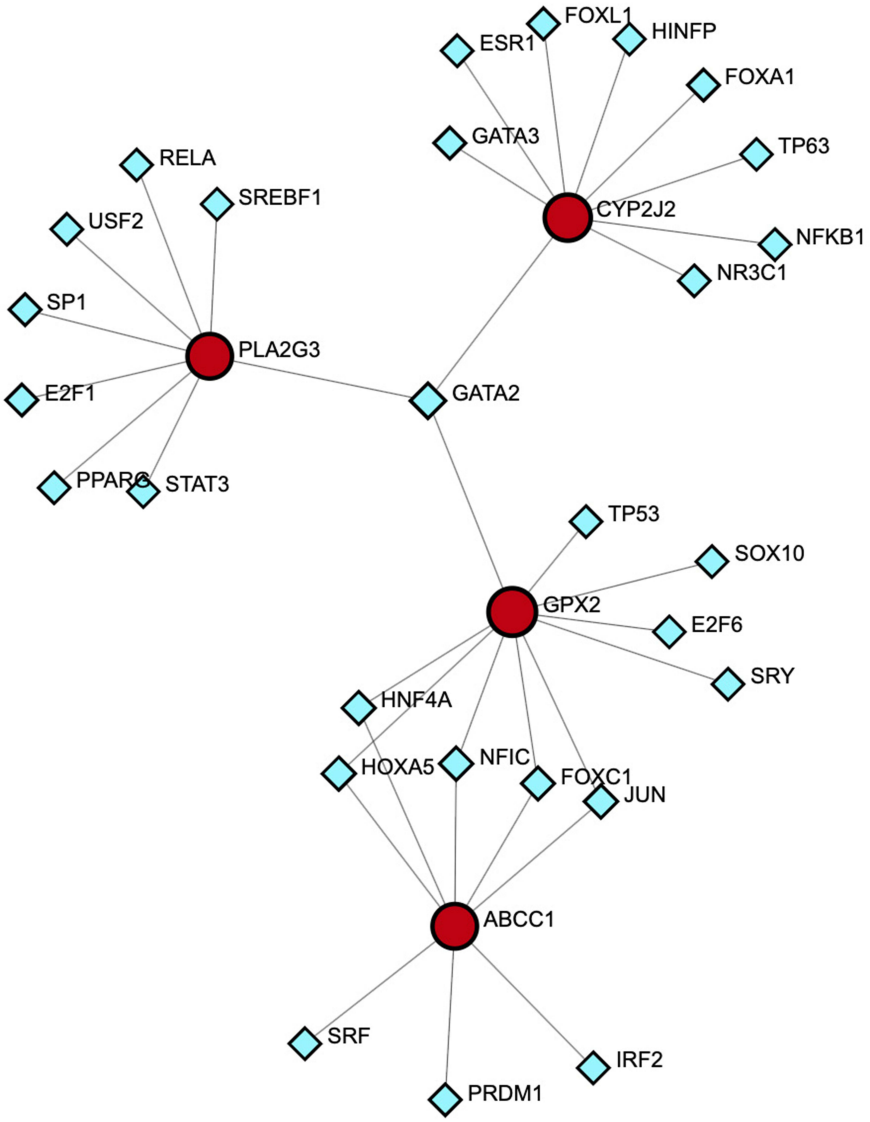

Figure 8 Transcription factor prediction analysis of key AAM genes. The transcription factor prediction analysis for *ABCC1*, *PLA2G3*, *CYP2J2*, and *GPX2* revealed shared regulatory transcription factors.

Functional enrichment analyses revealed the significant involvement of epidermis development, immune response, and inflammation in psoriasis, which is consistent with the histological changes observed in psoriatic lesions, such as epidermal hyperplasia and inflammatory cell infiltration.[27] The upregulation of interferon response pathways aligns with previous reports of Th1 and Th17 cell activation in psoriatic lesions.[28] Conversely, the downregulation of adipogenesis and bile acid metabolism pathways may be associated with the metabolic comorbidities frequently observed in psoriasis patients.[29,30]

Immune cell composition analysis demonstrated significantly increased infiltration of inflammatory cells, such as activated $CD4^+$ T cells (including Th1 and Th17), activated dendritic cells, and M1 macrophages, which is consistent with previous studies reporting the crucial role of immune cell infiltration in the pathogenesis of psoriasis.[31] The complex interplay between these infiltrating immune cells and keratinocytes creates a persistent inflammatory loop, perpetuating the aberrant differentiation and proliferation of keratinocytes, ultimately leading to the development and exacerbation of psoriasis plaques.[31,32]

The identification of key AAM genes and their associations with specific cellular processes, signaling pathways, and immune cell types in psoriasis provides novel insights into the molecular basis of the disease. *PLA2G3*, a member of the

phospholipase A2 family, catalyzes the release of arachidonic acid from membrane phospholipids, subsequently initiating the production of various inflammatory mediators.[33] Our study revealed that *PLA2G3* expression is upregulated in psoriatic lesions and positively correlates with epithelial-mesenchymal transition, mTORC1 signaling, MYC target genes, the p53 pathway, and PI3K/AKT/mTOR signaling, suggesting its potential role in promoting cell proliferation. Moreover, *PLA2G3* is positively associated with activated mast cells, consistent with previous studies demonstrating that mast cells can secrete *PLA2G3*, thereby promoting their maturation and contributing to the development of an anaphylaxis-sensitive phenotype.[34] *ABCC1*, the gene encoding multidrug resistance-associated protein 1, has been implicated in the efflux of inflammatory mediators and the regulation of immune cell function.[35] Our study found that *ABCC1* expression positively correlates with several cellular processes and signaling pathways, such as estrogen response, glycolysis, hypoxia, MYC target genes, and the p53 pathway. These correlations suggest that *ABCC1* may influence keratinocyte proliferation, differentiation, energy metabolism, and cell cycle progression in psoriatic lesions.[36–38] *CYP2J2*, a member of the cytochrome P450 superfamily, is involved in the metabolism of arachidonic acid to EETs, which possess anti-inflammatory properties.[39] In psoriatic lesions, *CYP2J2* expression is reduced, potentially leading to decreased EET synthesis and aggravated inflammatory responses.[40] *GPX2*, encoding glutathione peroxidase 2, plays a crucial role in the defense against oxidative stress and the maintenance of cellular redox homeostasis.[41] Our research revealed that *GPX2* expression positively correlates with interferon α and γ responses, suggesting its critical role in the resolution of inflammation and the cellular response to interferons.[42]

While our integrative bioinformatics approach has revealed novel insights into the role of AAM genes in psoriasis pathogenesis and immune dysregulation, certain limitations should be acknowledged. First, the findings are based on the analysis of publicly available transcriptomic datasets, and further experimental validation using targeted gene expression assays and functional studies is necessary to confirm the role of the identified key AAM genes in psoriasis. Second, the bioinformatics approach relies on statistical associations and correlations, and the directionality and mechanistic details of these relationships remain to be elucidated through functional studies. Despite these limitations, our study provides a strong foundation for future research on the role of AAM in psoriasis and highlights potential therapeutic targets and biomarkers. To further elucidate the role of AAM in psoriasis, future studies should focus on validating the key findings using multi-omics approaches, functional experiments, and clinical samples, paving the way for novel diagnostic and therapeutic strategies.

Conclusion

Our integrative bioinformatics analysis identified key AAM genes, including *ABCC1, PLA2G3, CYP2J2*, and *GPX2*, that are differentially expressed in psoriatic lesions and associated with specific cellular processes, signaling pathways, and immune cell types. These findings provide novel insights into the complex molecular mechanisms underlying psoriasis pathogenesis and immune dysregulation, and highlight potential therapeutic targets and biomarkers for the disease. Further research on the role of AAM in psoriasis is warranted to validate these findings and translate them into clinical applications for improved diagnosis and treatment of this chronic inflammatory skin disorder.

Ethics Approval and Consent to Participate

Our study was reviewed and approved by the Medical Ethics Committee of the People's Hospital of Chongqing Liangjiang New Area (approval number: 1).

Consent for Publication

All authors read and approved the final manuscript.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the Suzhou Science and Education Strong Health Project (grant numbers QNXM2024002).

Disclosure

The authors declare no competing of interest.

References

1. Parisi R, Iskandar IY, Kontopantelis E, et al. National, regional, and worldwide epidemiology of psoriasis: systematic analysis and modelling study. *BMJ*. 2020;369. doi:10.1136/bmj.m1590
2. Griffiths CE, Armstrong AW, Gudjonsson JE, et al. Psoriasis. *Lancet*. 2021;397(10281):1301–1315. doi:10.1016/S0140-6736(20)32549-6
3. Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. *Lancet*. 2007;370(9583):263–271. doi:10.1016/S0140-6736(07)61128-3
4. Singh S, Taylor C, Kornmehl H, et al. Psoriasis and suicidality: a systematic review and meta-analysis. *J Am Acad Dermatol*. 2017;77(3):425–440.e422. doi:10.1016/j.jaad.2017.05.019
5. Nowowiejska J, Baran A, Flisiak I. Aberrations in lipid expression and metabolism in psoriasis. *Int J Mol Sci*. 2021;22(12):6561. doi:10.3390/ijms22126561
6. Hanna VS, Hafez EAA. Synopsis of arachidonic acid metabolism: a review. *J Adv Res*. 2018;11:23–32. doi:10.1016/j.jare.2018.03.005
7. Shores DR, Binion DG, Freeman BA, et al. New insights into the role of fatty acids in the pathogenesis and resolution of inflammatory bowel disease. *Inflamm Bowel Dis*. 2011;17(10):2192–2204. doi:10.1002/ibd.21560
8. Wang T, Fu X, Chen Q, et al. Arachidonic acid metabolism and kidney inflammation. *Int J Mol Sci*. 2019;20(15):3683. doi:10.3390/ijms20153683
9. Luo Y, Jin M, Lou L, et al. Role of arachidonic acid lipoxygenase pathway in Asthma. *Prostaglandins Other Lipid Mediat*. 2022;158:106609. doi:10.1016/j.prostaglandins.2021.106609
10. Hammarström S, Hamberg M, Samuelsson B, et al. Increased concentrations of nonesterified arachidonic acid, 12L-hydroxy-5, 8, 10, 14-eicosatetraenoic acid, prostaglandin E2, and prostaglandin F2alpha in epidermis of psoriasis. *Proc Natl Acad Sci*. 1975;72(12):5130–5134. doi:10.1073/pnas.72.12.5130
11. Barr R, Wong E, Mallet A, et al. The analysis of arachidonic acid metabolites in normal, uninvolved and lesional psoriatic skin. *Prostaglandins*. 1984;28(1):57–65. doi:10.1016/0090-6980(84)90113-8
12. Ruzicka T, Simmet T, Peskar BA, et al. Skin levels of arachidonic acid-derived inflammatory mediators and histamine in atopic dermatitis and psoriasis. *J Invest Dermatol*. 1986;86(2):105–108. doi:10.1111/1523-1747.ep12284061
13. Brain S, Camp R, Dowd P, et al. The release of leukotriene B4-like material in biologically active amounts from the lesional skin of patients with psoriasis. *J Invest Dermatol*. 1984;83(1):70–73. doi:10.1111/1523-1747.ep12261712
14. Nair RP, Duffin KC, Helms C, et al. Genome-wide scan reveals association of psoriasis with IL-23 and NF-κB pathways. *Nat Genet*. 2009;41(2):199–204. doi:10.1038/ng.311
15. Kim J, Bissonnette R, Lee J, et al. The spectrum of mild to severe psoriasis vulgaris is defined by a common activation of IL-17 pathway genes, but with key differences in immune regulatory genes. *J Invest Dermatol*. 2016;136(11):2173–2182. doi:10.1016/j.jid.2016.04.032
16. Yao Y, Richman L, Morehouse C, et al. Type I interferon: potential therapeutic target for psoriasis? *PLoS One*. 2008;3(7):e2737. doi:10.1371/journal.pone.0002737
17. Ritchie ME, Phipson B, Wu D, et al. limma powers differential expression analyses for RNA-sequencing and microarray studies. *Nucleic Acids Res*. 2015;43(7):e47–e47. doi:10.1093/nar/gkv007
18. Kolde R. Pheatmap: pretty heatmaps. *R Package Version*. 2019;1(2):726.
19. Wickham H, Wickham H. *Data Analysis*. Springer; 2016.
20. Yu G, Wang L-G, Han Y, et al. clusterProfiler: an R package for comparing biological themes among gene clusters. *Omics*. 2012;16(5):284–287. doi:10.1089/omi.2011.0118
21. Langfelder P, Horvath S. WGCNA: an R package for weighted correlation network analysis. *BMC Bioinf*. 2008;9:1–13. doi:10.1186/1471-2105-9-559
22. Friedman J, Hastie T, Tibshirani R. Regularization paths for generalized linear models via coordinate descent. *J Stat Softw*. 2010;33(1):1. doi:10.18637/jss.v033.i01
23. Meyer D, Dimitriadou E, Hornik K, et al. e1071: misc functions of the department of statistics, probability theory group (formerly: E1071), TU Wien. *R Package Version*. 2019;1(2).
24. Breiman L. Random forests. *Mach Learn*. 2001;45:5–32. doi:10.1023/A:1010933404324
25. Hänzelmann S, Castelo R, Guinney J. GSVA: gene set variation analysis for microarray and RNA-seq data. *BMC Bioinf*. 2013;14:1–15. doi:10.1186/1471-2105-14-7
26. Newman AM, Liu CL, Green MR, et al. Robust enumeration of cell subsets from tissue expression profiles. *Nat Methods*. 2015;12(5):453–457. doi:10.1038/nmeth.3337
27. Yamanaka K, Yamamoto O, Honda T. Pathophysiology of psoriasis: a review. *J Dermatol*. 2021;48(6):722–731. doi:10.1111/1346-8138.15913
28. Li B, Huang L, Lv P, et al. The role of Th17 cells in psoriasis. *Immunol Res*. 2020;68:296–309. doi:10.1007/s12026-020-09149-1
29. Wei G, Shi Z, Wu X, et al. The emerging potential of bile acids as a modulator of psoriatic inflammation. *J Psoriasis Psoriatic Arthritis®*. 2023;8(3):118–123. doi:10.1177/24755303231177965
30. Kiełbowski K, Bakinowska E, Ostrowski P, et al. The role of adipokines in the pathogenesis of psoriasis. *Int J Mol Sci*. 2023;24(7):6390. doi:10.3390/ijms24076390
31. Kamata M, Tada Y. Crosstalk: keratinocytes and immune cells in psoriasis. *Front Immunol*. 2023;14:1286344. doi:10.3389/fimmu.2023.1286344
32. Kamata M, Tada Y. Dendritic cells and macrophages in the pathogenesis of psoriasis. *Front Immunol*. 2022;13:941071. doi:10.3389/fimmu.2022.941071
33. Murakami M, Sato H, Taketomi Y. Updating phospholipase A2 biology. *Biomolecules*. 2020;10(10):1457. doi:10.3390/biom10101457

34. Taketomi Y, Ueno N, Kojima T, et al. Mast cell maturation is driven via a group III phospholipase A2-prostaglandin D2–DP1 receptor paracrine axis. *Nat Immunol*. 2013;14(6):554–563. doi:10.1038/ni.2586
35. Kotlyarov S, Kotlyarova A. Clinical significance of lipid transport function of ABC transporters in the innate immune system. *Membranes*. 2022;12 (11):1083. doi:10.3390/membranes12111083
36. Zhou T, Yang Z, Chen Y, et al. Estrogen accelerates cutaneous wound healing by promoting proliferation of epidermal keratinocytes via Erk/Akt signaling pathway. *Cell Physiol Biochem*. 2016;38(3):959–968. doi:10.1159/000443048
37. Wen T, Tingting L, Fangfang L, et al. HIF-1α may promote glycolysis in psoriasis vulgaris via upregulation of CD147 and GLUT1. *J Cent South Univ Med Sci*. 2021;46(4):333. doi:10.11817/j.issn.1672-7347.2021.200010
38. Wang H, Guo M, Wei H, et al. Targeting p53 pathways: mechanisms, structures, and advances in therapy. *Signal Transduct Target Ther*. 2023;8 (1):92. doi:10.1038/s41392-023-01347-1
39. Sisignano M, Steinhilber D, Parnham MJ, et al. Exploring CYP2J2: lipid mediators, inhibitors and therapeutic implications. *Drug Discovery Today*. 2020;25(9):1744–1753. doi:10.1016/j.drudis.2020.07.002
40. Aradhyula V, Breidenbach JD, Khatib-Shahidi BZ, et al. Transcriptomic analysis of arachidonic acid pathway genes provides mechanistic insight into multi-organ inflammatory and vascular diseases. *Genes*. 2024;15(7):954. doi:10.3390/genes15070954
41. Pei J, Pan X, Wei G, et al. Research progress of glutathione peroxidase family (GPX) in redoxidation. *Front Pharmacol*. 2023;14:1147414. doi:10.3389/fphar.2023.1147414
42. Hiller F, Besselt K, Deubel S, et al. GPx2 induction is mediated through STAT transcription factors during acute colitis. *Inflamm Bowel Dis*. 2015;21(9):2078–2089. doi:10.1097/MIB.0000000000000464