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ORIGINAL RESEARCH

Identification of PRKCQ-AS1 as a Keratinocyte-Derived Exosomal lncRNA That Promotes Th17 Differentiation and IL-17 secretion in Psoriasis Through Bioinformatics, Machine Learning Algorithms, and Cell Experiments

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Background: Psoriasis is an immune-mediated skin disease where Th17 cell differentiation and IL-17 secretion play critical roles. This study investigates key exosomal ncRNAs regulating the Th17/IL-17 axis in psoriasis and their mechanisms.

Methods: We integrated bulk RNA sequencing datasets from the GEO database to construct and evaluate exosome-related patterns. Subsequently, exosome-related ncRNAs in psoriasis lesions were identified primarily through weighted gene co-expression network analysis and five machine learning algorithms. Additionally, large-scale integrated single-cell RNA sequencing data and genome-wide association study (GWAS) data were included to investigate the mechanisms of key ncRNA, primarily through immune infiltration analysis, gene set enrichment analysis (GSEA), co-expression analysis, and Mendelian randomization. Finally, the mechanisms of key ncRNA were confirmed primarily through cell co-culture and lentiviral transfection, assessed by immunofluorescence, qRT-PCR, and Western blot.

Results: We identified 10 exosome-related ncRNAs, including PRKCQ-AS1, and constructed five machine learning models with excellent diagnostic performance, emphasizing PRKCQ-AS1's significance. Mendelian randomization demonstrated a causal relationship between PRKCQ-AS1 and psoriasis. Immune infiltration analysis and GSEA indicated that PRKCQ-AS1 influences the infiltration pattern of $CD4^+$T cells, promotes Th17 differentiation, and is related to STAT3. The expression distribution in single-cell RNA sequencing data suggested that exosomal PRKCQ-AS1 may originate from keratinocytes, and co-expression analysis supported its role in STAT3 activation within lymphocytes. Co-culture experiments confirmed that keratinocytes in psoriasis models, as well as keratinocytes overexpressing PRKCQ-AS1, can upregulate PRKCQ-AS1 levels in $CD4^+$T cells via exosomes, promoting Th17 cell differentiation and IL-17 secretion. Consistent results and STAT3 signaling pathway activation were detected in $CD4^+$T cells overexpressing PRKCQ-AS1.

Conclusion: PRKCQ-AS1 is an exosomal lncRNA from keratinocytes in psoriasis, promoting Th17 differentiation and IL-17 secretion through STAT3 activation. This finding deepens the understanding of psoriasis pathogenesis and provides a basis for targeted therapies.

Keywords: psoriasis, exosomes, Th17, PRKCQ-AS1, pathogenesis, bioinformatics

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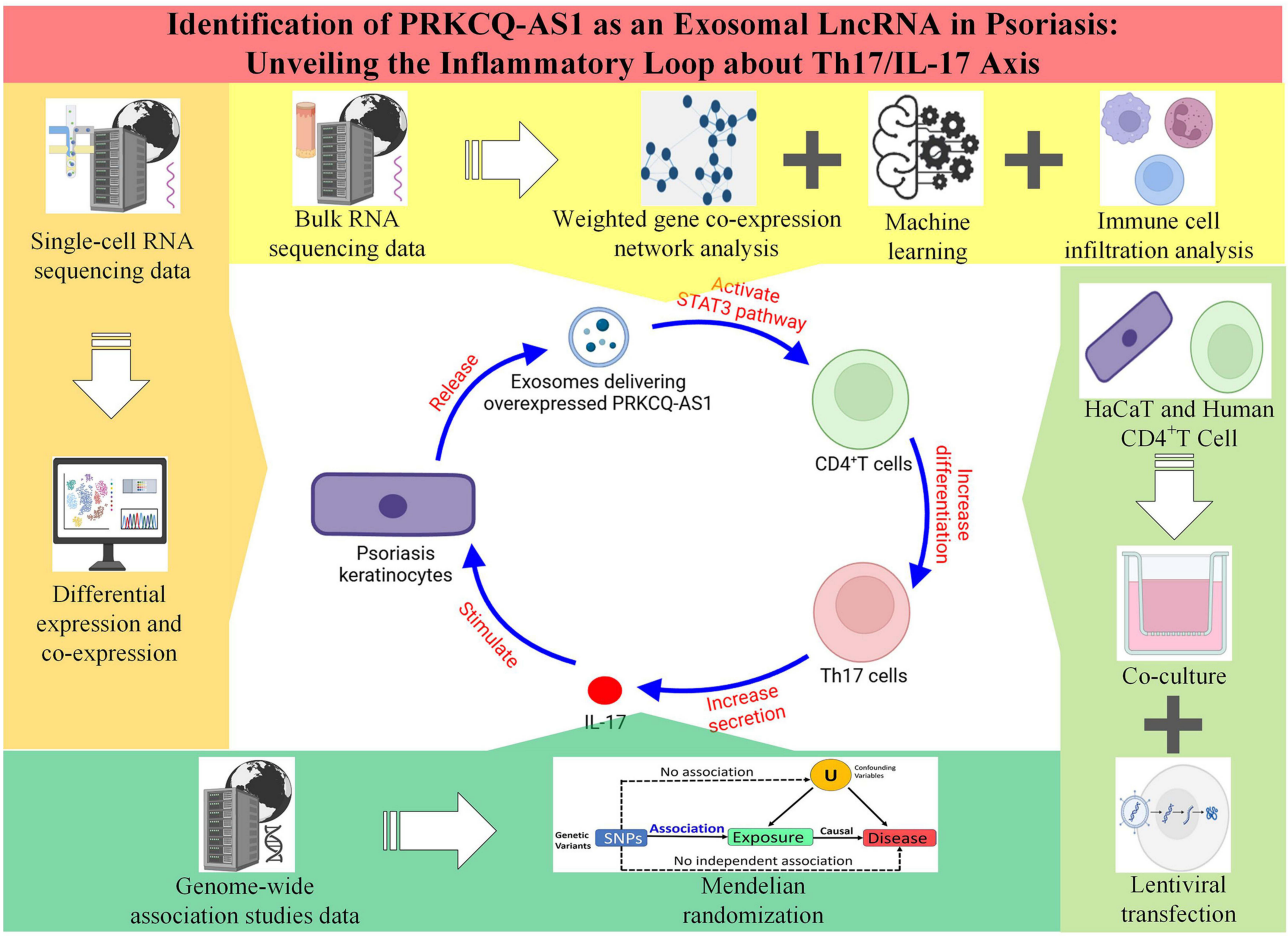
Graphical Abstract



Introduction

Psoriasis is an immune-mediated inflammatory skin disease characterized by the excessive proliferation and abnormal differentiation of keratinocytes, resulting in well-defined erythematous plaques covered with silvery scales. Given the challenges in clinical treatment, particularly the high recurrence rate, psoriasis significantly impacts patients' physical and mental health, reducing their quality of life.[1] It is believed that the key aspect of psoriasis pathogenesis lies in immune system dysregulation, encompassing the intricate cross-talk among dendritic cells, macrophages, neutrophils, B cells, and T cells, which is primarily manifested as the abnormal differentiation and dysfunction of $CD4^+$T lymphocytes.[2]

In psoriasis, the dysregulation of the differentiation and function of CD4+ T cell subsets is notably complex. Research indicates that a shift in the Th1/Th2 differentiation balance toward Th1 plays a pivotal role in psoriasis, primarily by amplifying cutaneous inflammation via the abnormal expression of IFN-γ, TNF-α and IL-4.[3–5] As a result of over-production of TNF-α, patients with psoriasis display elevated levels of Th22 cells and plasma IL-22, which are positively correlated with disease severity; elevated IL-22 levels may result in various outcomes, including the inhibition of keratinocyte differentiation.[6] Among $CD4^+$T cells, Th17 cells play a crucial role in psoriasis.[7] Once activated, Th17 cells release inflammatory cytokines such as TNF-α and IL-17, which promote the infiltration of inflammatory cells and the hyperproliferation of keratinocytes, leading to the formation of psoriatic plaques.[8,9]

In the treatment of psoriasis, biologics such as adalimumab,[10] secukinumab,[11] and ustekinumab,[12] which respectively target and inhibit TNF-α, IL-17, and IL-12/IL-23, are effective therapeutic drugs in addition to traditional treatment methods such as glucocorticoids, vitamin D derivatives, calcineurin inhibitors, and phototherapy. These biologics are generally superior to traditional methods in alleviating psoriasis symptoms, supporting the crucial role of Th17 cell differentiation and functional abnormalities in psoriasis.[13] However, the potential risks of systemic infections and tumors associated with these biologics need to be carefully considered.[14] Therefore, locally inhibiting Th17 cell differentiation and subsequent cytokine secretion in psoriatic lesions may be a promising therapeutic strategy to avoid systemic adverse effects.[15] Investigating the mechanisms of abnormal Th17 cell differentiation or activation in psoriatic lesions remains of significant value.

Exosomes, a type of extracellular vesicle measuring between 30 −150 nm, play a significant role in intercellular communication, including immune system regulation.[16] Exosomes contain a variety of biologically active molecules, including proteins, microRNAs (miRNAs), and long non-coding RNAs (lncRNAs), which are not only responsible for the biological functions of exosomes but also act as key indicators of the state of their originating cells.[17] In recent years, the roles and mechanisms of exosomes in immune system regulation and psoriasis have gradually attracted attention. Studies have shown that lncRNAs carried by exosomes can regulate the functions of immune cells. For example, tumor cell-derived exosomes can transport lncRNAs in colorectal cancer, affecting the differentiation of $CD4^+$T cells into Th17 cells, thereby promoting IL-17 secretion.[18] Indeed, evidence of abnormal exosome secretion or abnormal content within exosomes can also be found in psoriasis.[19–21]

As one type of the key components in exosomes, lncRNAs are a class of non-coding RNA with a transcription length greater than 200 nucleotides and various biological functions.[22] In recent years, numerous studies have shown that abnormal expression or dysfunction of lncRNAs is widespread in immune diseases. For example, mutations in lncRNA RMRP can promote the formation of the DDX5-RORγt complex, enhance the differentiation of Th17 cells, and increase IL-17A expression, contributing to the development of Th17 cell-mediated inflammatory diseases.[23] LncRNA NEAT1 is highly expressed in peripheral blood mononuclear cells and $CD4^+$T cells of rheumatoid arthritis patients. Knocking down NEAT1 can inhibit Th17 cell differentiation.[24] lncRNA GAS5 is expressed at low levels in the plasma and $CD4^+$T cells of systemic lupus erythematosus patients, and it inhibits $CD4^+$T cell activation by releasing miR-92a-3p's target gene E4BP4.[25]

Is there exosome-derived lncRNA in psoriasis lesions that promotes $CD4^+$T cell differentiation into Th17 cells and IL-17 secretion, ultimately advancing the progression of psoriasis? Research on this topic is limited.

In this study, we initially utilized bulk RNA sequencing data and identified that the highly expressed lncRNA PRKCQ-AS1 in psoriasis lesions is closely associated with exosomes through methods such as constructing and validating exosome-related pattern characterization, weighted gene co-expression network analysis (WGCNA), machine learning and others. Subsequently, based on bulk RNA sequencing, single-cell RNA sequencing, and GWAS data, we mainly employed methods such as GSEA, immune infiltration analysis, and Mendelian randomization to discover that psoriasis keratinocytes may transmit overexpressed PRKCQ-AS1 through exosomes, activate the STAT3 signaling pathway, and promote $CD4^+$T cell differentiation into Th17 cells and IL-17 secretion. Finally, we validated the aforementioned conclusion through cell experiments. The organization and design of the research are illustrated (Figure 1). This study expands our understanding of the regulation of Th17 cells by keratinocytes and their exosomes in psoriasis, elucidates the role of PRKCQ-AS1 in psoriasis, and enriches the upstream pathways of Th17 cell differentiation and IL-17 secretion, offering new potential for the development of therapies with higher tissue selectivity for psoriasis treatment.

Materials and Methods

Data Acquisition

Three bulk RNA sequencing datasets of psoriasis and the corresponding clinical data were obtained from the National Center for Biotechnology Information (NCBI) Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo/). Briefly, GSE13355(update date 2020–03-12) includes 64 cases of normal skin tissue from normal samples (NN), 58 cases of

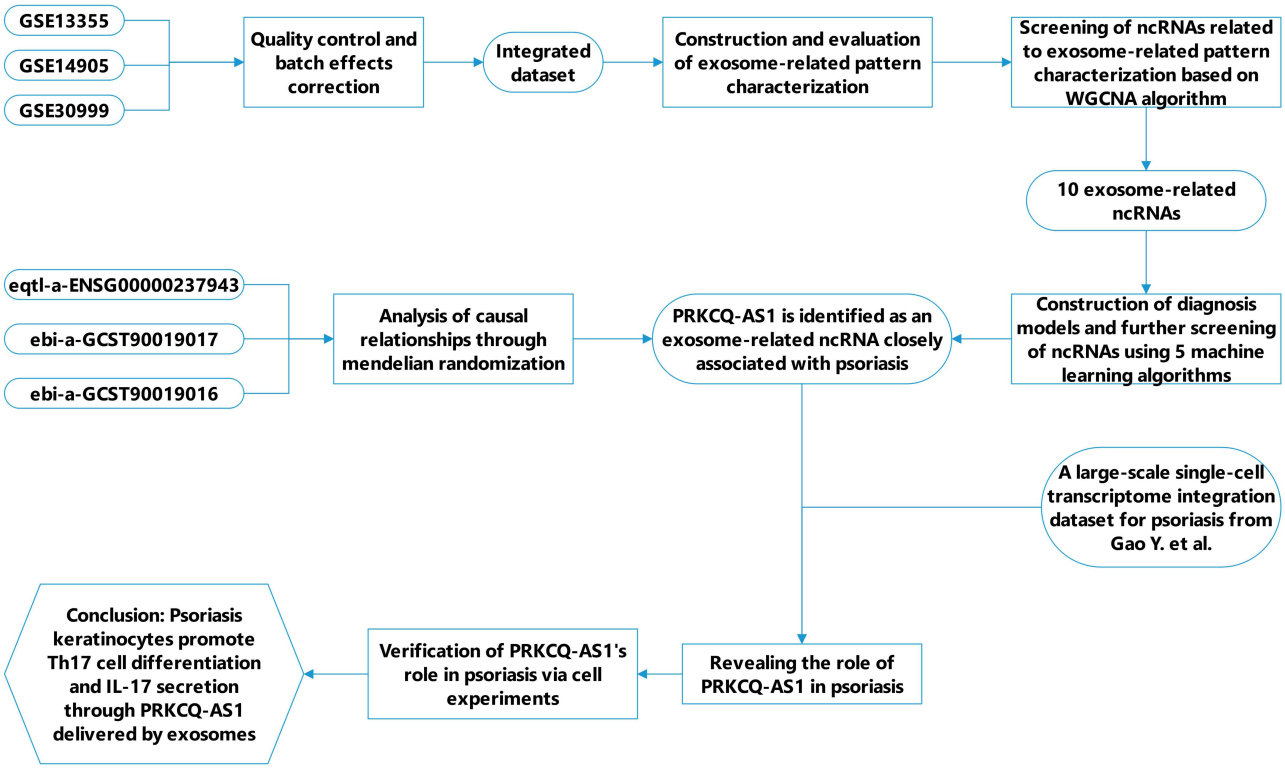


Figure 1 Work flow of the study. This figure provides a concise overview of the entire research process.

normal skin tissue from patients with psoriasis (PN), and 58 cases of psoriasis lesions from patients with psoriasis (PP); GSE14905(update date 2019–03-25) consists of 21 cases of NN, 28 cases of PN, and 33 cases of PP; GSE30999(update date 2019–03-25) comprises 85 cases each of PN and PP. All three datasets mentioned above are based on the Affymetrix Human Genome U133 Plus 2.0 Array (GPL570) platform. GWAS datasets (acquisition data 2023–11-23) of psoriasis and PRKCQ-AS1 expression Quantitative Trait Loci (eQTL) were obtained from the Integrative Epidemiology Unit (IEU) OPEN GWAS database (https://gwas.mrcieu.ac.uk/). Among them, ebi-a-GCST90019017 contains information on 8,470,172 Single Nucleotide Polymorphisms (SNPs); ebi-a-GCST90019016 contains information on 8,536,277 SNPs; eqtl-a-ENSG00000237943 includes information on 21,494 SNPs. The gmt files (download date 2024–10-24) containing gene set information for GSEA were queried from the Molecular Signatures Database (https://www.gsea-msigdb.org/gsea/). A large-scale single-cell RNA sequencing integration dataset of psoriasis was referenced from Gao Y. et al's study (publication date 2023–09-26).[26] The 125 exosome-related genes used for constructing exosome-related pattern characterization were summarized by Peng W. et al's study (publication date 2023–03-16).[27] The biomarkers of STAT3 signaling pathway for reflecting the activation were collected from literature.[28–39]

Quality Control and Batch Effect Correction of Bulk RNA Sequencing Datasets

To obtain reliable results, larger dataset were aimed to be used for subsequent analysis instead of a single dataset. Therefore, the three bulk RNA sequencing datasets were merged and batch effects were corrected as need. The R package "SVA" (version 3.42.0) was primarily used to eliminate batch effects among GSE13355, GSE14905, and GSE30999. Sample nature (non-lesions or lesions) was considered to assist in batch effect correction. The R package "FactoMineR" (version 2.11) was used for principal component analysis (PCA) to quantify the distribution of dataset samples, assisting in evaluating the quality of individual datasets and controlling batch effects in the integrated dataset. Data visualization was primarily accomplished using the R package "ggplot2" (version 3.5.1).

Establishment and Assessment of Exosome-Related Pattern Characterization

The construction and assessment methods of exosome-related pattern characterization were adapted from Peng W. et al's study.[27] Specifically, 119 genes (listed in Table S1, 6 genes without clear annotations in the integrated dataset were excluded) associated with exosome biogenesis and secretion, as well as exosome markers obtained from the literature, were used to construct the exosome-related pattern characterization based on the integrated bulk RNA sequencing dataset using PCA. The first principal component was defined as exosome-related PCA scores (PEXS), serving as the quantitative indicator for the exosome-related pattern characterization of samples. The GSEA for assessing PEXS utilized the R package "fgsea" (version 1.20.0), with the gene set files obtained as mentioned above. Other assessment methods for PEXS were based on basic R functions.

Immune Cell Infiltration Analysis

To evaluate the immune levels of samples in the integrated bulk RNA sequencing dataset, the R package "CIBERSORT" (version 0.1.0) was primarily used. Based on the Leukocyte Signature Matrix for 22 immune cell types provided in the package, the infiltration levels of these cell types in all samples were calculated for subsequent statistical analyses.

Identification of ncRNAs Associated with Exosomes Through WGCNA

The WGCNA method was used to preliminarily screen exosome-related ncRNAs. Specifically, the ncRNAs were first annotated, and those with excessive missing data or zero variance were removed. Following the standard WGCNA workflow, we constructed a weighted co-expression network using the R package "WGCNA" (version 1.72–5). To ensure that the network satisfies the scale-free topology criteria, power values from 1 to 10 were examined in increments of 1, applying a commonly used R^2 threshold of 0.8. Based on these assessments, the optimal soft threshold was determined to be 5, corresponding to an R^2 value of 0.803. The adjacency matrix was then converted into a topological overlap matrix. Clustering analysis was performed to identify and merge ncRNA co-expression modules. Subsequently, the association between the modules and exosomes was evaluated using PEXS as the quantitative indicator. Core modules were filtered with an absolute module correlation greater than 0.4 with PEXS. ncRNAs within core modules were filtered with a positive Gene Significance (GS) and Module Membership (MM) over 0.8. The correlation between GS and MM was calculated to assess the consistency between the modules and PEXS.

Differential Gene Expression Analysis

Differential expression analysis of genes was performed by grouping samples according to different criteria based on specific needs. Specifically, when evaluating the expression changes of ncRNAs in psoriasis lesions, the grouping was based on the nature of the samples. For evaluating PEXS, the differential expression analysis before GSEA was based on the level of PEXS. To reveal the roles of PRKCQ-AS1 and STAT3 through GSEA, the differential expression analysis were based on the expression levels of the respective genes. The R package "limma" (version 3.50.3) was utilized for the specific analysis procedure to calculate gene expression differences between groups. As the process of screening genes via differential expression analysis was not involved, there was no need to manually set screening thresholds.

Construction and Feature Selection of Diagnosis Models Based on Machine Learning

To further screen ncRNAs closely related to psoriasis from those closely related to PEXS, GSE30999 was used as the training set, and GSE13355 as well as GSE14905 were used as the testing sets. Five machine learning algorithms were employed for modeling and further ncRNA screening. Specifically, in the training set, the Least Absolute Shrinkage and Selection Operator (LASSO) regression was first used for further variable selection of ncRNAs from the WGCNA screening results. Subsequently, LASSO, eXtreme Gradient Boosting (XGBoost), Random Forest (RF), Gradient Boosting Machine (GBM), and Light Gradient Boosting Machine (LGBM) were used to construct diagnosis models for psoriasis. Receiver Operating Characteristic (ROC) and Area Under the Curve (AUC) were used as model performance evaluation metrics, with model performance primarily optimized through grid tuning. The testing sets were used to evaluate the universality of the models. Finally, the "permutation cost" of features in the models was

calculated as a unified measure of feature importance across different models, thereby evaluating the contribution of ncRNAs in each psoriasis diagnosis model. SHapley Additive exPlanations (SHAP) helped in elucidating the impact of features on the results and in interpreting machine learning models. This section mainly utilized the following R packages: "glmnet" (version 4.1–8), "xgboost" (version 1.6.0.1), "randomForest" (version 4.7–1.1), "gbm" (version 2.1.8.1), "lightgbm" (version 3.3.5), "DALEX" (version 2.4.3), and "shapviz" (version 0.9.6).

Mendelian Randomization (MR) Analysis

eqtl-a-ENSG00000237943 was utilized as the exposure data, and ebi-a-GCST90019017 as well as ebi-a-GCST90019016 were utilized as the outcome data for MR analysis. MR must satisfy three core assumptions: (1) The association assumption, which posits a strong correlation between the SNP and the exposure; (2) The independence assumption, which asserts that the SNP is not related to the outcome through confounding pathways; (3) The exclusion assumption, which states that the SNP does not directly affect the outcome, but only indirectly through the exposure. To meet these core assumptions, the "TwoSampleMR" (version 0.6.8) and "biomaRt" (version 2.50.3) packages were employed to extract and filter cis-eQTL from the PRKCQ-AS1 eQTL data, with clumping parameters set to $P<5\times 10^{-8}$ and $r^2=0.01$, ensuring the strong correlation with exposure and independence of instrumental variables (IVs), also mitigating the impact of linkage disequilibrium. SNPs incompatible between exposures and outcomes were excluded. Positive strand alleles for palindromic SNPs were inferred using allele frequencies, and the palindromic SNPs were excluded if allele frequencies were unavailable. In the primary MR analysis, a meta-analysis of the estimates was conducted using Inverse Variance Weighting (IVW), MR-Egger, weighted mode, weighted median, and simple mode models. When all SNPs met the core assumptions of valid instrumental variables, the IVW method was applicable, and under these conditions, the IVW results were the most reliable. Consequently, IVW served as the primary test in the study, while the results from the other four methods provided supplementary information. The "mr_heterogeneity" function was employed to assess SNP heterogeneity, and the "mr_pleiotropy_test" function was utilized to evaluate horizontal pleiotropy.

Single-Cell Transcriptome Data Analysis

The large-scale integrated single-cell RNA sequencing dataset of psoriasis from Gao Y. et al[26] was employed as the data foundation for this study. The expression changes of PRKCQ-AS1 in various cell types within psoriasis lesions were extracted from the preliminary analysis results summarized by the authors in the original study. Cell clustering and co-expression in lymphocytes were analyzed and visualized using the "CellInfo vs GeneExpr" and "Gene coexpression" modules of the online analysis tools provided by the original study.

Cell Culture and Modeling

Immortalized human keratinocytes (HaCaT) (Immocell Biotechnology, China) were cultured in DMEM containing 10% fetal bovine serum and 1% penicillin-streptomycin. Human $CD4^+$T cells (Immocell Biotechnology, China) were cultured using a specialized medium (Immocell Biotechnology, China). The incubator was set to 37°C with 5% CO_2. HaCaT cells were stimulated with 20 ng/mL TNF-α for 12 h to establish a psoriasis-like keratinocyte model.[40] Following modeling, qRT-PCR was used to detect marker expression to confirm the successful establishment of the model.[41] Additionally, for cells requiring inhibition of exosome secretion, the exosome inhibitor GW4869 was added to the culture and incubated for 30 min before proceeding with subsequent experiments. The time for culturing with exosomes was 24 h.

Transwell Co-Culture System

A co-culture system was constructed using 0.4 μm pore transwell chambers (Sigma-Aldrich, USA). In the construction of the co-culture system, 5×10^4 HaCaT cells were seeded in the upper chamber, which was then inserted into the lower chamber seeded with 1×10^5 $CD4^+$T cells. After 24 h of co-culture, subsequent experiments were carried out. If HaCaT cells had been pre-treated before co-culture, they were washed twice with phosphate-buffered saline (PBS) to prevent pre-treatment reagents from directly affecting the co-culture results.

Transfection of Cell Lines

The vectors for overexpressing PRKCQ-AS1 and their corresponding negative controls were constructed by Sangon Biotech (China). Lentiviruses were packaged in HEK-293T (Wuhan Pricella Biotechnology, China) using Lipofectamine 3,000 (ThermoFisher, USA) according to the manufacturer's instructions. For cell transfection, cells were first seeded into 6-well plates, and virus along with 5 μg/mL polybrene sulfate (Beyotime, China) was added and incubated for 8 h. Then, the medium was replaced with the original cell culture medium and cultured for 24 h. 10 μg/mL puromycin (Beyotime, China) was used to select stable transfected cell lines. qRT-PCR was used to confirm the transfection efficiency.

Exosome Extraction

The extraction of exosomes followed the VEX Exosome Isolation Reagent (Vazyme, China) usage guidelines. In brief, the cell culture medium was collected and filtered through a 0.22 μm filter, and the resulting filtrate was transferred to a new centrifuge tube. The supernatant was collected after centrifugation at 3,000g for 20 min at 4°C. 1/3 volume of VEX Exosome Isolation Reagent was added to the supernatant, mixed until the sample was uniformly clear again, and the tube was placed vertically in a 4°C refrigerator for 16 h. Finally, centrifugation was performed at 10,000g for 30 min at 4°C to obtain the exosome pellet, which was resuspended in PBS for use.

Quantitative Real-Time Polymerase Chain Reaction (qRT-PCR)

According to the reagent usage guidelines, RNA was extracted from cells using the Cell/Tissue Total RNA Isolation Kit V2 (Vazyme, China). Reverse transcription was performed using the HiScript III 1st Strand cDNA Synthesis Kit (Vazyme, China). qRT-PCR was conducted using the Taq Pro Universal SYBR qPCR Master Mix (Vazyme, China). The PCR reaction protocol is detailed in Table 1. GAPDH was used as an internal control, and the $2^{-\Delta\Delta CT}$ method was employed to calculate the expression differences of target genes between samples. The primer sequences used can be found in Table S2.

Enzyme-Linked Immunosorbent Assay

For the cell supernatant, after the cell culture or co-culture experiment was completed, a specific volume of cell culture medium was aspirated and centrifuged at 4°C, 1,000g for 20 min. The supernatant was collected for detection. For cells, after the experiment was completed, they were washed three times with cold PBS. Every 10^6 cells were resuspended in 200μL of PBS containing protease inhibitor and lysed by sonication. The extract was centrifuged at 4°C, 1,500g for 10 min, and the supernatant was collected for detection. The detection was performed according to the instructions of the Human TNF-α ELISA Kit (COIBO BIO, China) and Human IL-17 ELISA Kit (COIBO BIO, China).

Table 1 The Reaction Process of qRT-PCR

Stage	Objective	Cycles	Temperature	Duration
Stage 1	Pre-denaturation	1	95°C	30 sec
Stage 2	Cycling reaction	40	95°C	10 sec
			60°C	10 sec
Stage 2	Melting curve	1	95°C	15 sec
			65°C	60 sec
			95°C	15 sec

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Immunofluorescence

Cells were gently rinsed with PBS and fixed with 4% paraformaldehyde for 20 min. They were then permeabilized with 0.25% Triton-X-100 for 20 min, followed by blocking with goat serum for 30 min. Recombinant anti-CD4 antibody (Abcam, UK) and monoclonal IL-17A antibody (Proteintech, China) were added as primary antibodies and incubated overnight at 4°C. Subsequently, fluorescent secondary antibodies Alexa Fluor 488 goat anti-rabbit IgG (Thermo Fisher, USA) and Alexa Fluor 568 goat anti-mouse IgG (Thermo Fisher, USA) were added and incubated in the dark at room temperature for 1 h. Finally, observations were conducted under a fluorescence microscope. Between the steps of fixation, permeabilization, blocking, and primary and secondary antibody incubations, cells were washed three times with PBS or Tris-buffered saline containing Tween-20 (TBST), as appropriate.

Western Blot

Each group of cell cultures was first treated with tissue/cell lysis buffer containing protease and phosphatase inhibitors. After thorough lysis, the samples were centrifuged at 12,000 g for 5 min at 4°C, and the supernatant was immediately transferred to a pre-cooled EP tube, resulting in the extracted cell protein. The protein concentration was determined using the bicinchoninic acid assay (BCA) method. Proteins were separated using SDS gel electrophoresis, transferred to a polyvinylidene fluoride (PVDF) membrane, and blocked with a rapid blocking solution for 30 min. Then, STAT3 Antibody (ThermoFisher, USA), Phospho-STAT3 Antibody (ThermoFisher, USA), Anti-IL-6 antibody (Abcam, UK), and Western Antibody GAPDH-Loading Control (Bioss, China) were used as primary antibodies and incubated overnight at 4°C. The membrane was washed three times with TBST, followed by incubation with Goat Anti-Rabbit IgG H&L/HRP (Bioss, China) and Goat Anti-Mouse IgG H&L/HRP (Bioss, China) as secondary antibodies at room temperature for 2 h. After washing three times with TBST, the membrane was treated with ECL luminescent solution (NCM Biotech, China) for 3 min, and then detected using a chemiluminescence imaging system.

Statistical Analysis

Statistical analysis of the data was primarily conducted and visualized using R (version 4.1.2), R Studio (version 2023.06.2 Build 561), and GraphPad Prism 9 (Version 9.5.1).Comparisons between two groups were conducted using T tests or Wilcoxon tests based on the specific conditions of the data according to statistical principles. A P-value less than 0.05 was considered statistically significant. "****", "***", "**" and "*" represent p-values of less than 0.0001, 0.001, 0.01, and 0.05, respectively.

Results

Data Review, Quality Control, and Batch Effect Correction

The distribution of gene expression in samples within GSE13355, GSE14905, and GSE30999 is shown (Figure 2A–C). The gene expression distribution within the GSE14905 and GSE30999 datasets shows good consistency. The PCA visualization results are shown (Figure 2D–F). There are significant differences in gene expression patterns between non-lesional (including NN and PN) and lesional (including PP) samples, which are consistent across the three bulk RNA sequencing datasets. The above findings support the rationality for merging the datasets. The PCA visualization results based on dataset or sample characteristics before and after batch correction are shown (Figure 2G–J). It can be seen that the expression patterns of the three datasets are significantly inconsistent before batch correction, and the PCA results based on sample characteristics are also unreadable. After batch correction, the expression patterns of the three datasets show high consistency, and the PCA results based on sample characteristics also present significant differences in expression patterns between non-lesional and lesional samples (Figure 2D–F). The gene expression distribution within the merged dataset after batch correction shows good consistency (Figure 2K). In summary, we have performed checks and quality control on the bulk RNA sequencing datasets before proceeding to the next analysis step, particularly effectively removing batch effects.

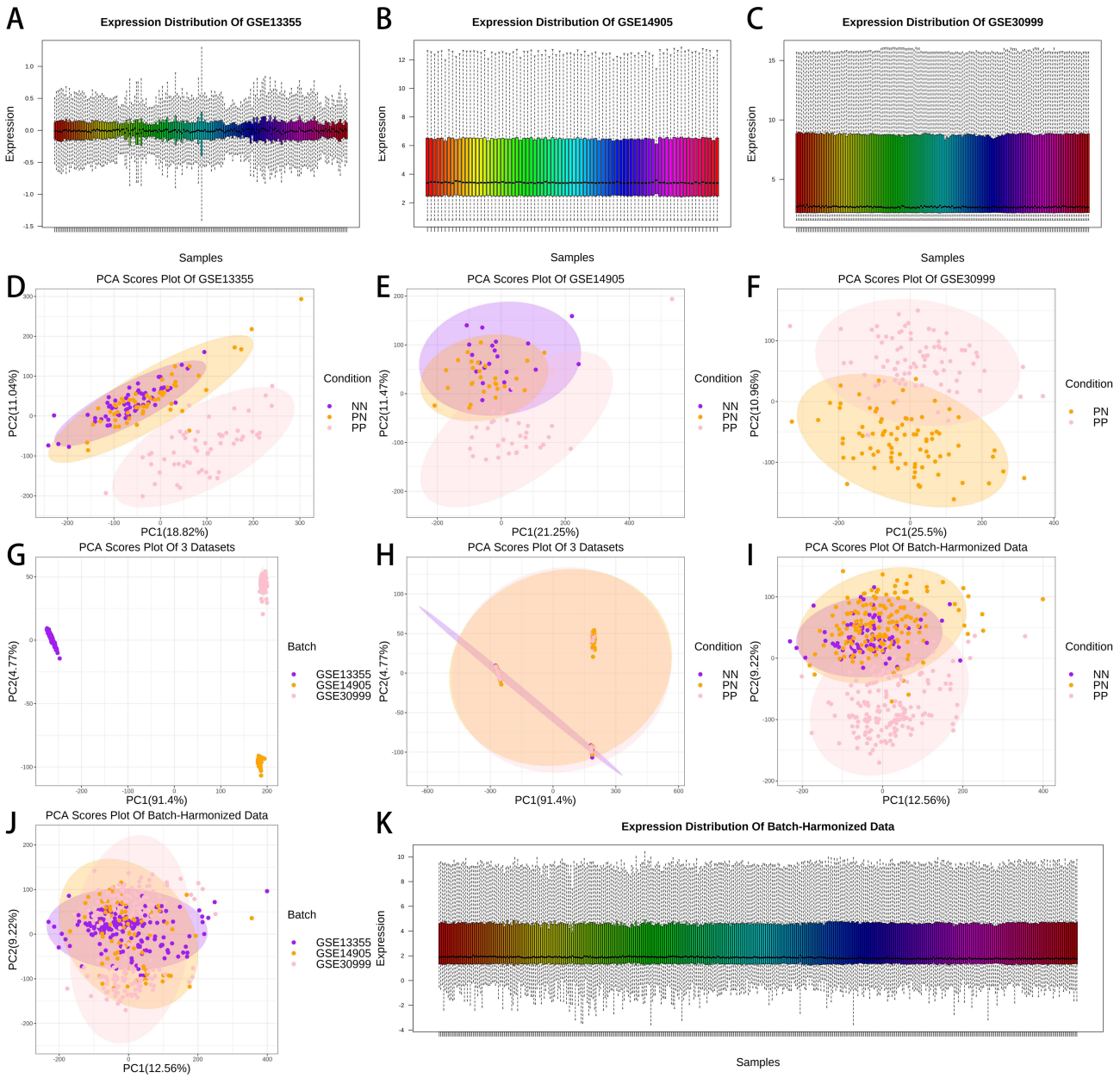

Figure 2 Quality control and correction of batch effects in bulk RNA-seq datasets. (**A**–**C**) Gene expression distribution in samples from GSE13355, GSE14905, and GSE30999. (**D**–**F**) PCA result visualization based on sample nature in GSE13355, GSE14905, and GSE30999. (**G** and **H**) PCA visualization results based on dataset or sample characteristics before batch correction. (**I** and **J**) PCA visualization results based on sample characteristics or dataset after batch correction. (**K**) Gene expression distribution in the integrated dataset after batch effect correction.

Construction and Evaluation of Exosome-Related Pattern Characterization

To reveal the exosome-related pattern in psoriasis lesion, we performed PCA analysis based on the integrated bulk RNA-seq dataset using exosome-related genes as described above (Figure 3A). In line with the literature, the first principal component accounted for a significantly higher proportion of the total variance than other components, and was therefore designated as PEXS. GSEA results indicated that several exosome-related biological processes (BP) and cellular components (CC) were significantly enriched in the high PEXS group (Figure 3B,C and Table S3), and PEXS was significantly positively correlated with the expression of typical exosome markers TSG101, HSPA8, PDCD6IP, and FLOT2 (Figure 3D), demonstrating the reliability of PEXS. PEXS showed significant differences between non-lesional and lesional groups (Figure 3E), and PCA visualization using exosome-related genes demonstrated the differences

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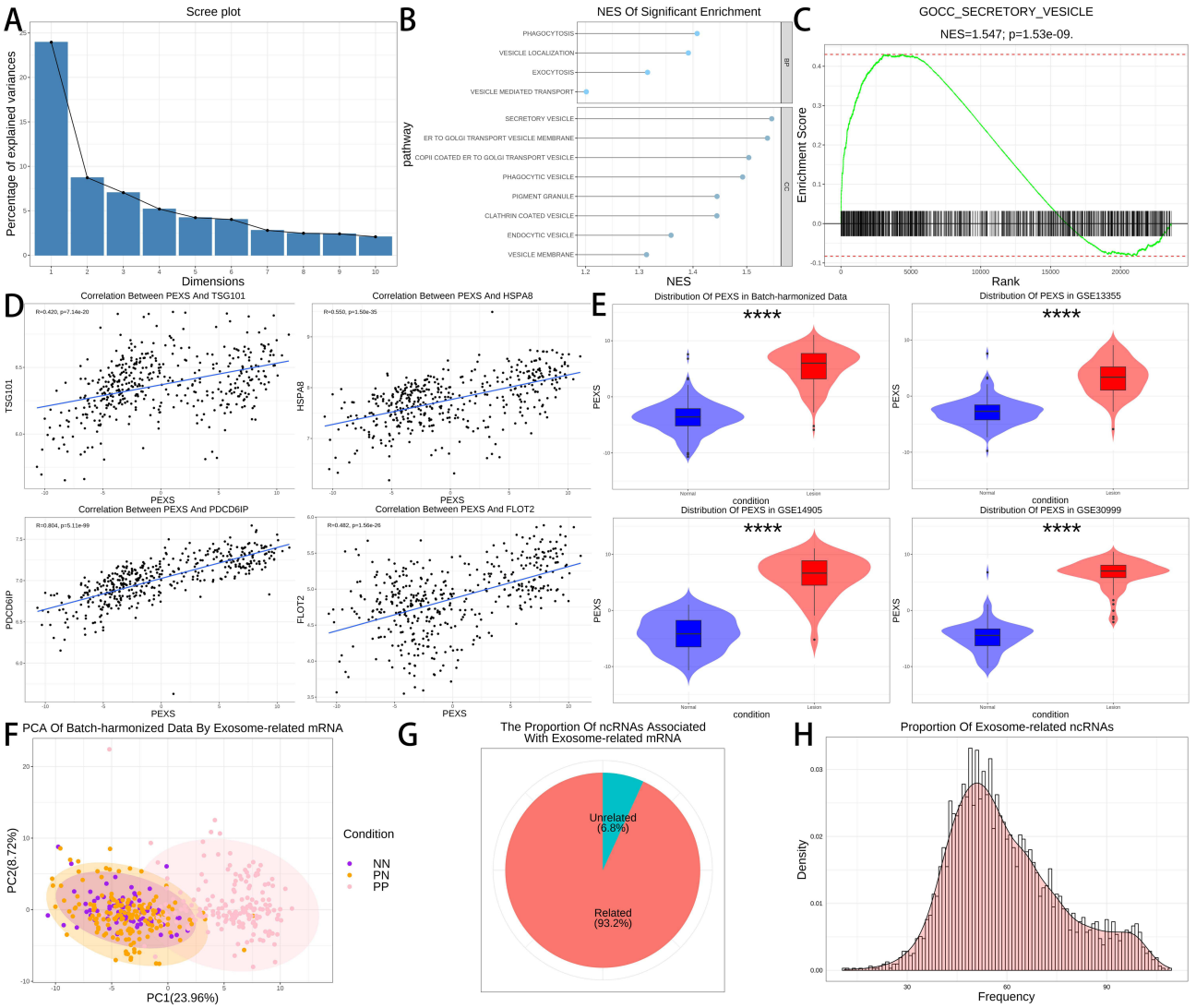

Figure 3 Construction and evaluation of exosome-related pattern characterization. (**A**) Percentage of variances explained by top 10 principal components. (**B**) Display of GSEA results of exosome-related BP and CC. (**C**) Individual display of GSEA result for GOCC_SECRETORY_VESICLE. (**D**) The correlation between PEXS and the expression of typical exosome markers. (**E**) The differences of PEXS between non-lesional and lesional in the integrated dataset, GSE13355, GSE14905, and GSE30999. (**F**) PCA visualization results using exosome-related genes in the integrated dataset. (**G**) The proportion of ncRNAs with at least one significant correlation pair with exosome-related genes. (**H**) The distribution of ncRNAs associated with different numbers of exosome-related genes. ****P < 0.0001.

between non-lesional and lesional samples (Figure 3F), supporting the close relationship between psoriasis and exosomes as well as the validity of PEXS. We further found that most ncRNAs were significantly correlated with at least one exosome-related gene (Figure 3G), and a small portion of ncRNAs were significantly correlated with almost all annotated exosome-related genes (Figure 3H), supporting the potential functional association of ncRNAs with exosomes in psoriasis.

PEXS Correlates with the Infiltration of Multiple Immune Cells

We calculated the infiltration of 22 types of immune cells in all samples of the integrated dataset and visualized the proportion of infiltrating cells in the low PEXS group (Figure 4A) and the high PEXS group (Figure 4B). By comparison, significant differences in the infiltration of various immune cells were found between the groups (Figure 4C), indicating that the regulation of multiple immune cells in psoriatic lesions is related to exosomes, including $CD4^{+}$T cells that we are concerned about.

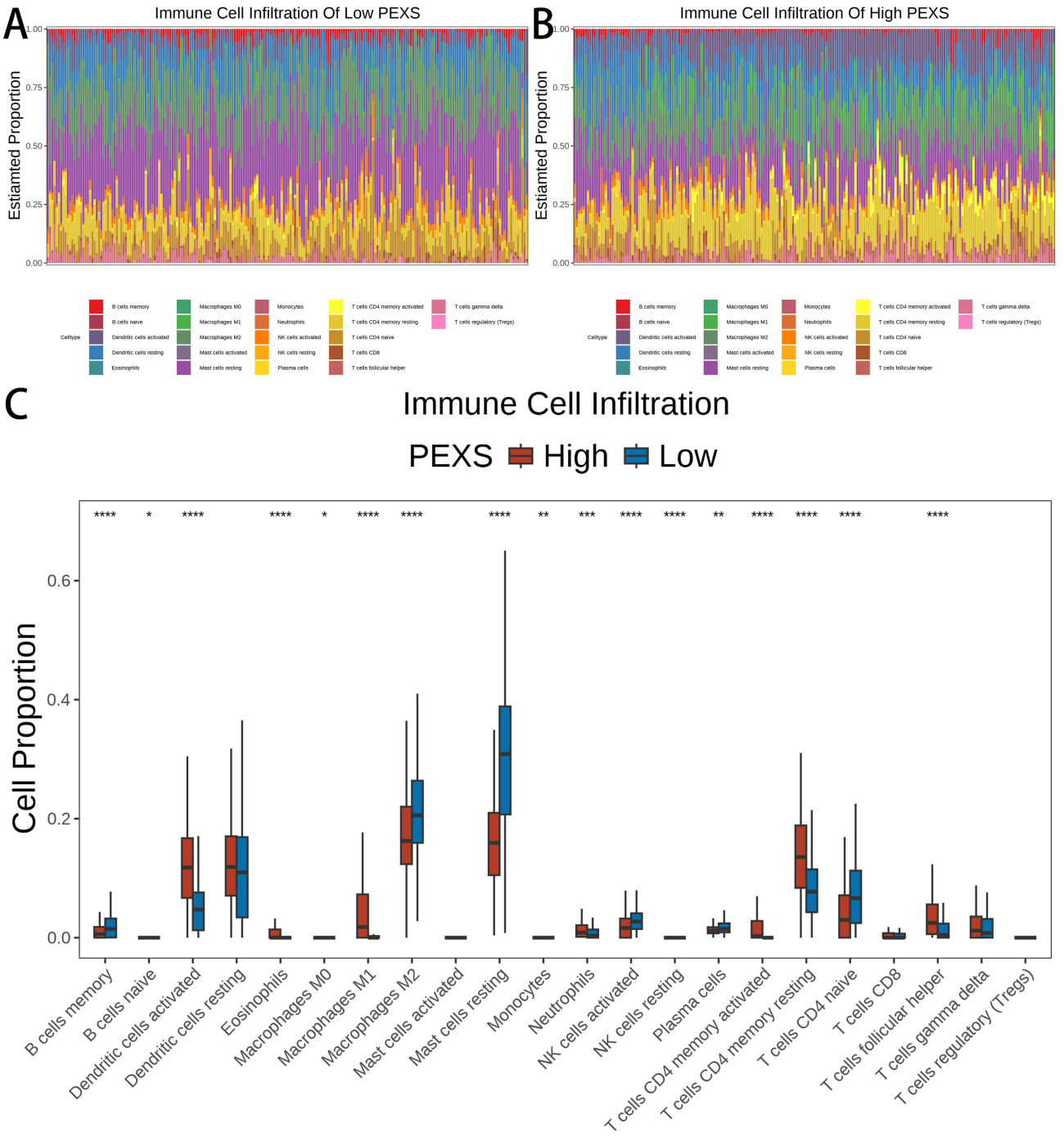

Figure 4 Immune cell infiltration in different PEXS conditions. (**A** and **B**) Immune cell infiltration in high PEXS group and low PEXS group. (**C**) Differences in immune cell infiltration between high PEXS and low PEXS groups. *: P < 0.05, **: P < 0.01, ***: P < 0.001, ****P < 0.0001.

Screening for ncRNAs Closely Related to Exosomes Using WGCNA

To accurately identify ncRNAs associated with exosomes, we used the WGCNA algorithm to construct a gene co-expression network from the ncRNA data of the integrated dataset. The selection of Power is shown (Figure 5A). We identified 17 modules in total, with their inter-module correlations displayed (Figure 5B). Among them, 8 modules showed a strong significant association with PEXS, which serves as a quantitative indicator of exosome-related pattern characterization (Figure 5C). The relationship between GS and MM within some modules is shown (Figure 5D). Through the screening described in the Methods section, 10 ncRNAs were identified as closely related to exosomes. The expression of these 10 ncRNAs showed significant

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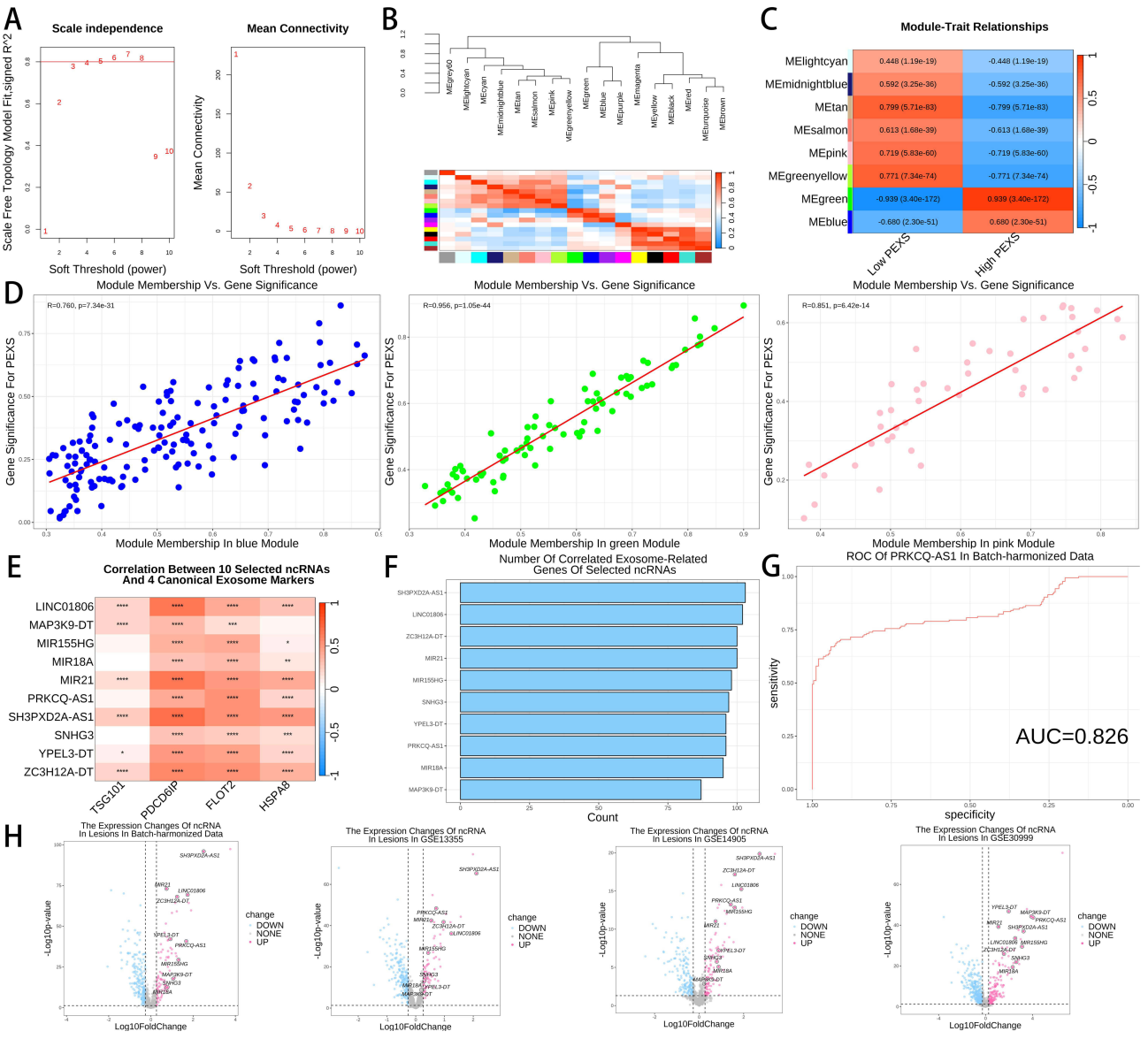

Figure 5 Screening of ncRNA closely related to PEXS through WGCNA. (**A**) Selection of power in WGCNA. (**B**) The relationship between co-expression modules. (**C**) Modules significantly related to PEXS. (**D**) Scatterplot of correlation between modules and PEXS. (**E**) Correlation heatmap between 10 ncRNAs and 4 typical exosome markers. (**F**) The significant correlation between 10 ncRNAs and 119 exosome-related genes. (**G**) ROC and AUC of PRKCQ-AS1 as a diagnosis biomarker for psoriasis. (**H**) Volcanic map of differential expression of 10 ncRNAs between non-lesions and lesions in the integrated dataset, GSE13355, GSE14905, and GSE30999. *: P < 0.05, **: P < 0.01, ***: P < 0.001, ****P < 0.0001.

correlations with the expression of 4 typical exosome markers (Figure 5E), and there were numerous correlated pairs with exosome-related genes we annotated (Figure 5F), supporting the association of these ncRNAs with exosomes. We plotted the ROC curve (AUC=0.826) to clarify that PRKCQ-AS1 has a high diagnostic value for psoriasis in integrated dataset (Figure 5G). The expression of these ncRNAs showed significant differences between non-lesional and lesional samples in the integrated dataset and three sub-datasets, although some ncRNAs had small fold changes (Figure 5H, Table S4).

Construction of Diagnosis Models and Feature Importance Evaluation Based on Machine Learning

To identify ncRNAs closely related to psoriasis from those associated with exosomes and evaluate their diagnosis performance as biomarkers, we constructed five diagnosis models using five machine learning algorithms and further identified three ncRNAs most closely related to psoriasis through feature importance evaluation. Before modeling, we

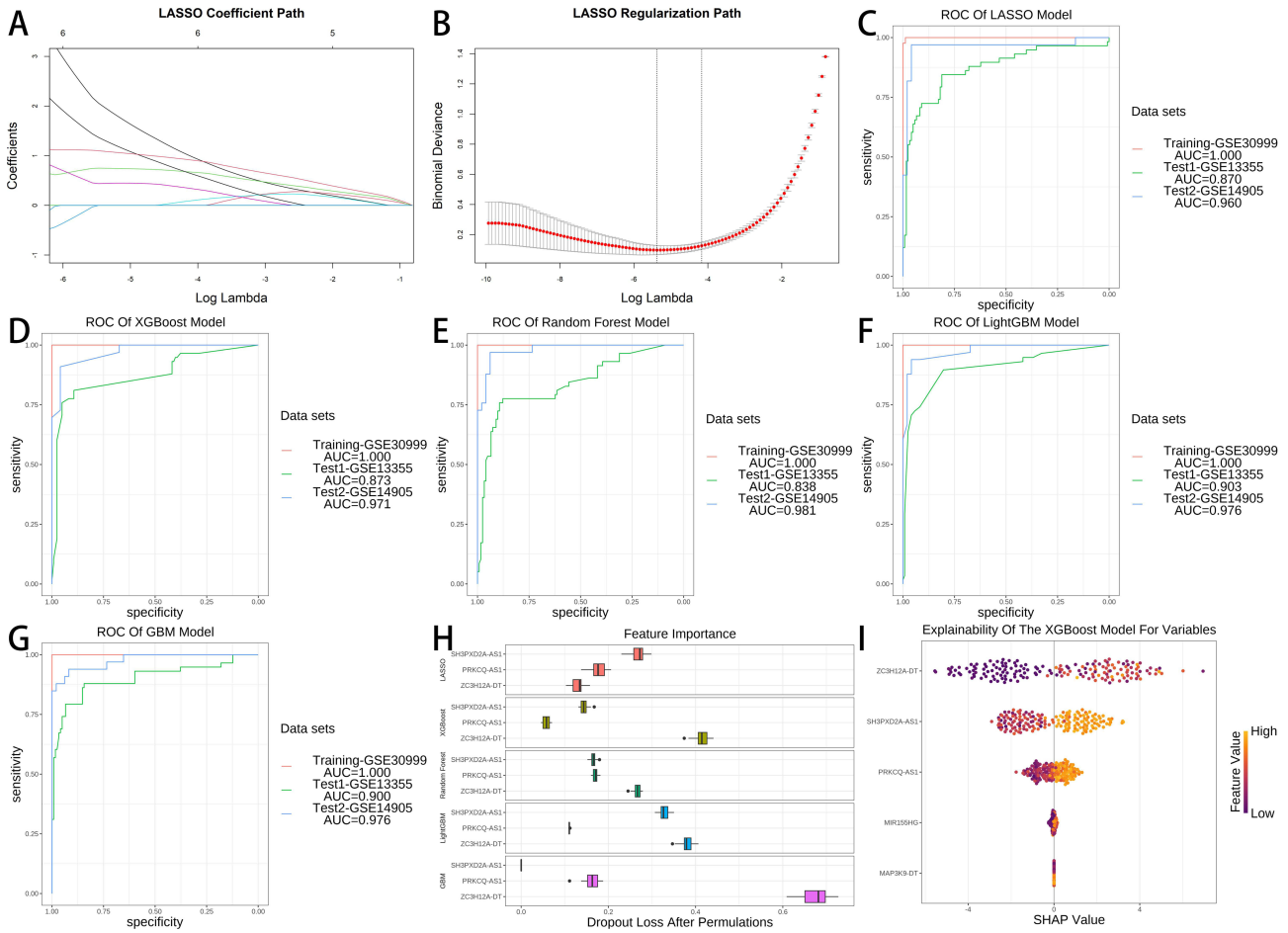

Figure 6 Construction of diagnosis model and evaluation of feature importance based on machine learning. (**A**) The variation characteristics of the coefficient of variables in the LASSO regression model. (**B**) The selection process of the optimum value of the parameter λ in the LASSO regression model by cross-validation method. (**C**–**G**) ROC and AUC of LASSO, XGBoost, RF, LightGBM and GBM models. (**H**) Dropout loss of three top variables in each diagnosis model in 16 repeated verifications. The higher the value, the more important the variable is for the accuracy of the diagnosis model. (**I**) Global explainability of the XGBoost model for variables (in order of importance based on the mean of absolute SHAP values). Without altering the conclusions, minor random perturbations are introduced into the SHAP values to improve the visualizations.

first performed further feature selection using LASSO (Figure 6A and B). Subsequently, we constructed diagnosis models to distinguish between non-lesional and lesional samples using machine learning. The evaluation results of the models showed that the performance of LASSO (Figure 6C), XGBoost (Figure 6D), RF (Figure 6E), LightGBM (Figure 6F), and GBM (Figure 6G) models was outstanding. The AUC of the five models reached 1.000 in the training set GSE30999, above 0.960 in the testing set GSE14905, and above 0.830 in the testing set GSE13355, suggesting the important value of these ncRNAs for psoriasis. Further quantification of feature importance revealed that PRKCQ-AS1, ZC3H12A-DT, and SH3PXD2A-AS1 were ranked among the top three in importance across the five models (Figure 6H), compelling us to believe in their role in psoriasis. We further explained the XGBoost model using SHAP and swarm plots, and the results showed that the high expression of these three ncRNAs helps push the model output towards a diagnosis of "psoriasis", which is consistent with our previous analysis results (Figure 6I).

Exploring the Causal Relationship Between PRKCQ-AS1 and Psoriasis Through Mendelian Randomization

We explored the causal relationship between PRKCQ-AS1 and psoriasis using MR. In the analysis using PRKCQ-AS1 cis-eQTL as exposure data and ebi-a-GCST90019017 as outcome data, we found a causal relationship between PRKCQ-AS1 expression and psoriasis, with PRKCQ-AS1 expression being a risk factor for psoriasis. The results were consistent across IVW, MR-Egger, weighted mode, weighted median, and simple mode models (Figure 7A). We also visualized the

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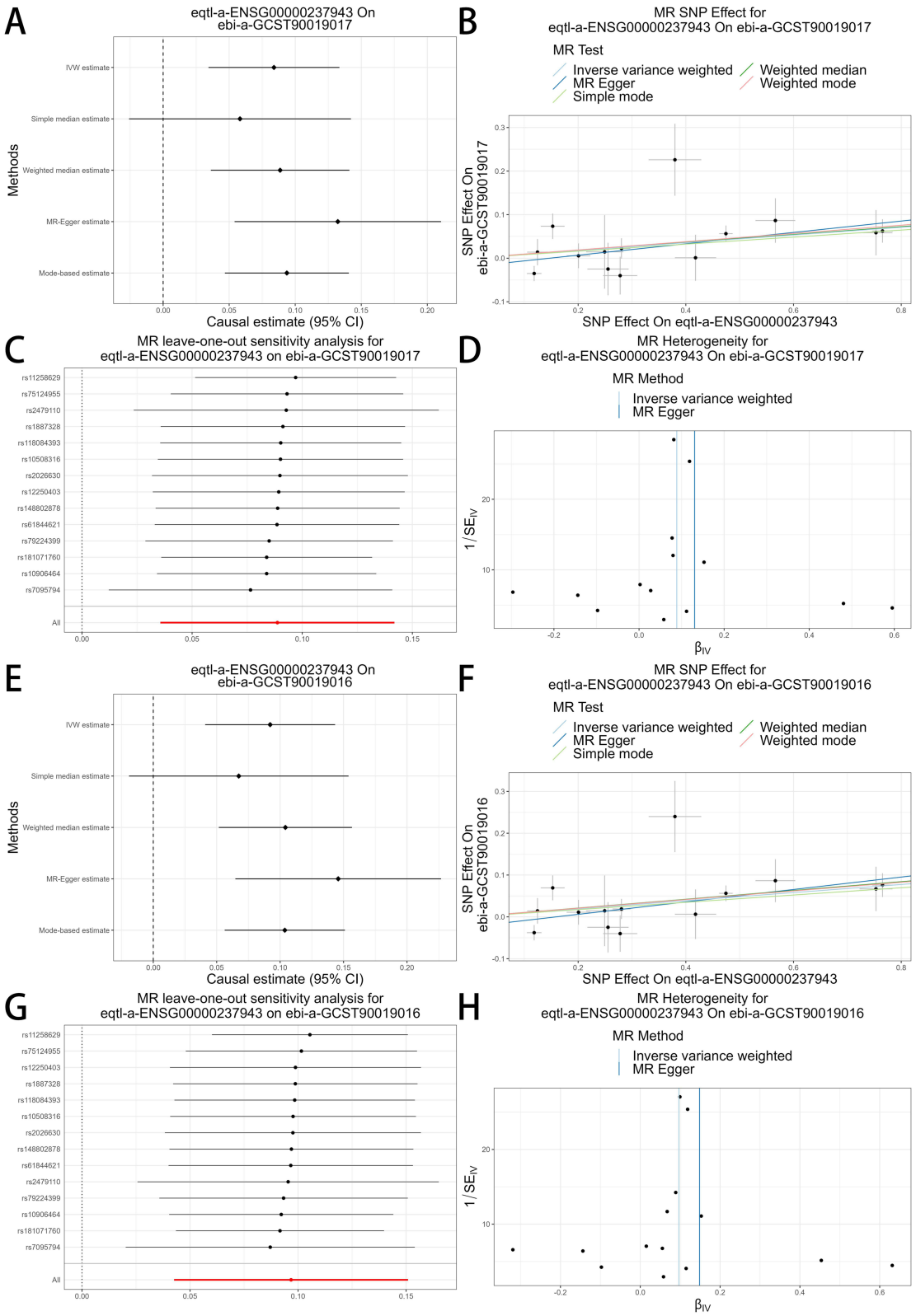

Figure 7 Exploring the causal relationship between PRKCQ-AS1 and psoriasis through Mendelian randomization. (**A** and **E**) Forest plot for causal effects of PRKCQ-AS1 (eqtl-a-ENSG00000237943) on psoriasis (ebi-a-GCST90019017 and ebi-a-GCST90019016) in 5 MR methods. (**B** and **F**) SNP effects in 5 MR methods. (**C** and **G**) Leave-one-out sensitivity analysis in MR. (**D** and **H**) Funnel plot illustrating the heterogeneity in MR.

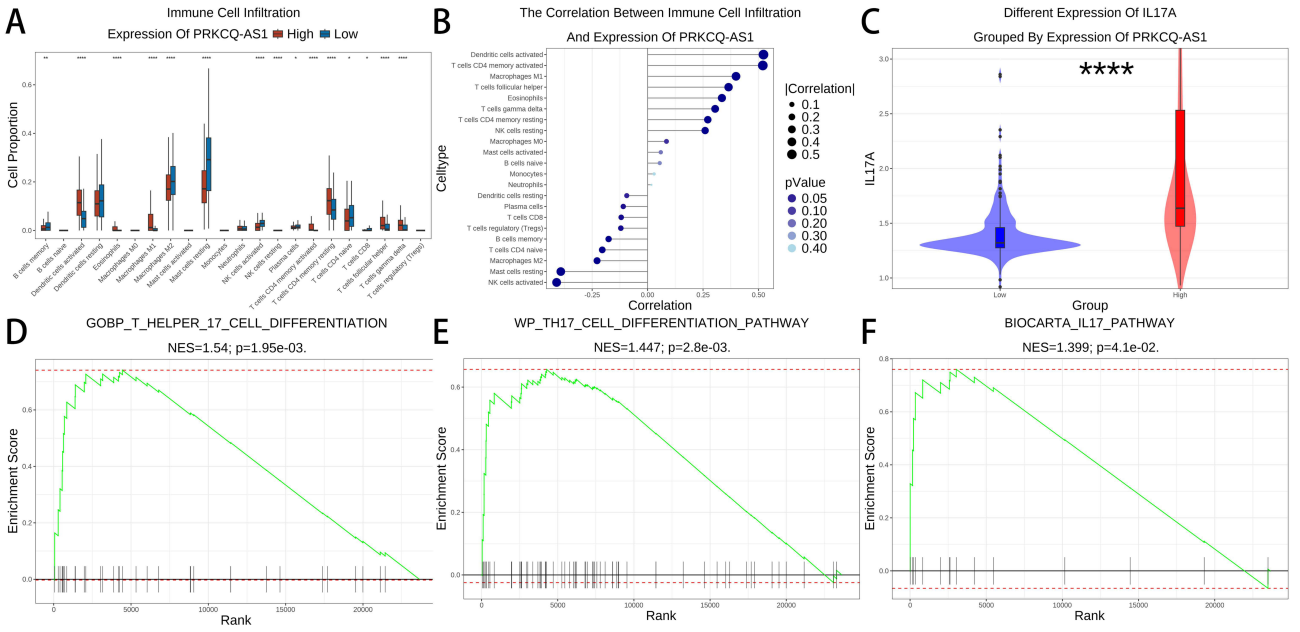

Figure 8 The expression of PRKCQ-AS1 is positively correlated with Th17 differentiation and IL-17 secretion. (**A**) The difference in immune cell infiltration between the high and low PRKCQ-AS1 groups. (**B**) The correlation between immune cell infiltration and PRKCQ-AS1 expression. (**C**) Differences in IL17A expression between high and low PRKCQ-AS1 groups. (**D** and **E**) The GSEA results of Th17 differentiation related pathways based on the expression of PRKCQ-AS1. (**F**) The GSEA results of IL-17 secretion based on the expression of PRKCQ-AS1. *: P < 0.05, **: P < 0.01, ****P < 0.0001.

impact of SNPs on the results of the five methods (Figure 7B). We performed quality control on MR using various methods and visualized the leave-one-out sensitivity analysis (Figure 7C) and plotted the funnel plot of SNPs (Figure 7D), showing no significant SNP heterogeneity or horizontal pleiotropy (Table S5), indicating reliable results. The MR analysis results using ebi-a-GCST90019016 as outcome data were consistent with the above (Figure 7E–H, Table S6).

Exploring the Role of PRKCQ-AS1 in Psoriasis

After establishing causality, we explored the potential role of PRKCQ-AS1 in psoriasis through various methods. Immunoinfiltration analysis indicated significant differences in $CD4^+$T cell infiltration patterns between the high and low PRKCQ-AS1 expression groups (Figure 8A), and PRKCQ-AS1 expression was significantly positively correlated with $CD4^+$T cell activation tendency (Figure 8B). We also found that IL17A expression was significantly higher in the high PRKCQ-AS1 expression group compared to the low expression group (Figure 8C). GSEA results showed that multiple Th17 differentiation-related pathways (Figure 8D, E and Table S3) and IL-17 secretion (Figure 8F, Table S3) gene sets were significantly positively enriched in the high PRKCQ-AS1 expression group. These data strongly suggest that PRKCQ-AS1 promotes Th17 differentiation and IL-17 secretion in psoriatic lesions.

Revelation of the Mechanism of PRKCQ-AS1 in Psoriasis

We conducted further research on the mechanism of PRKCQ-AS1 in promoting Th17 differentiation and IL-17 secretion. GSEA results indicated that gene sets related to STAT3 signaling pathway activation were significantly positively enriched in the high PRKCQ-AS1 expression group (Figure 9A,B and Table S3). Several STAT3 signaling pathway-related markers showed significant expression differences between the high and low PRKCQ-AS1 expression groups (Figure 9C), and were significantly correlated with PRKCQ-AS1 expression (Figure 9D), consistent with the characteristics of STAT3 signaling pathway activation. These results suggest that PRKCQ-AS1 may exert its regulatory effects by activating the STAT3 signaling pathway.

We further performed GSEA based on STAT3 expression, and the results showed that Th17 differentiation-related pathways significantly positively enriched in the high PRKCQ-AS1 expression group were also significantly positively

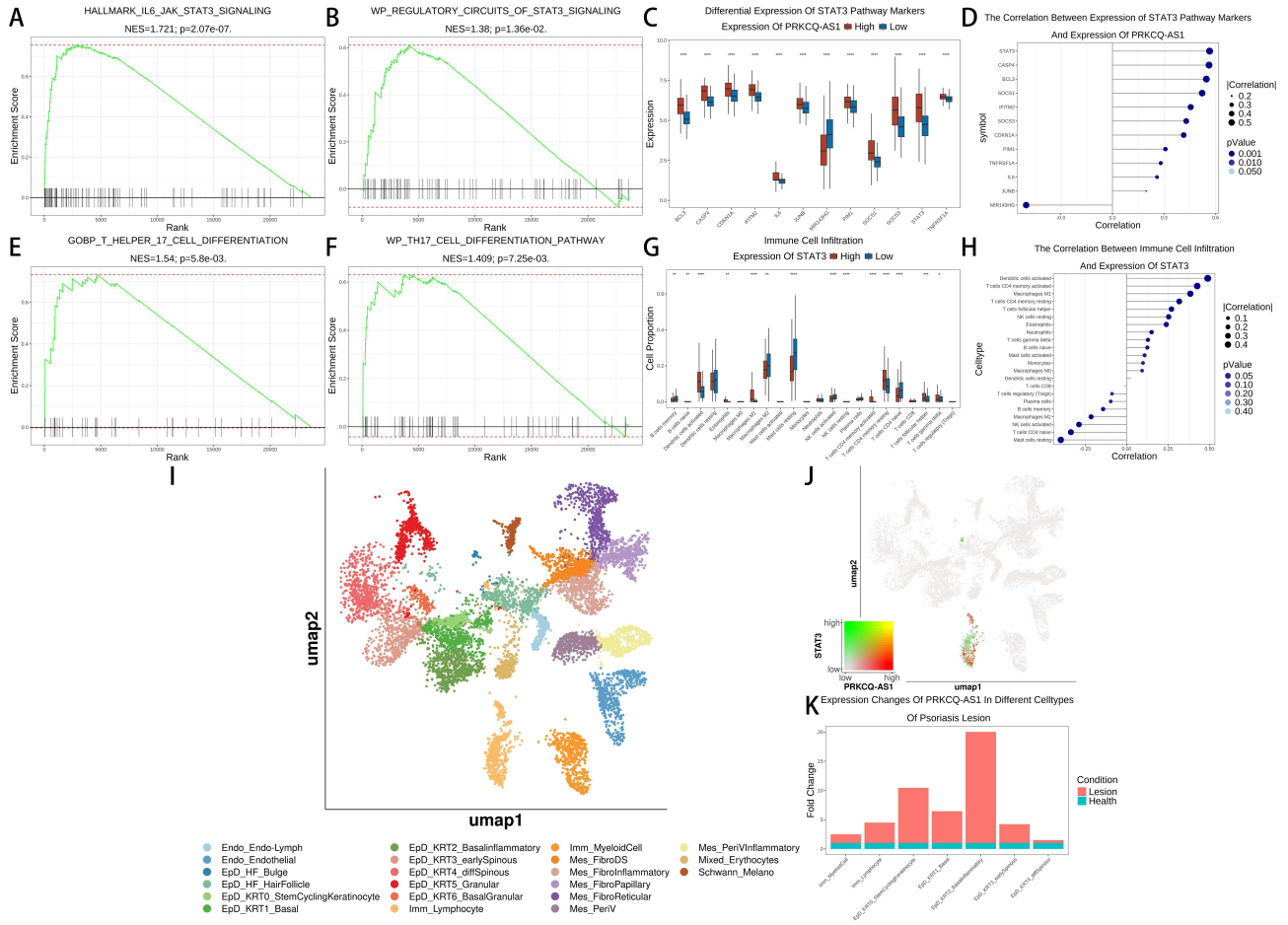

Figure 9 Possible regulatory mechanism of PRKCQ-AS1 on CD4$^+$T cells. (**A** and **B**) The GSEA results of STAT3 signaling pathways based on the expression of PRKCQ-AS1. (**C**) The different expression of STAT3 signaling pathway-related markers between the high and low PRKCQ-AS1 groups. (**D**) The correlation between the expression of STAT3 signaling pathway-related markers and PRKCQ-AS1. (**E** and **F**) The GSEA results of Th17 differentiation related pathways based on the expression of STAT3. (**G**) The difference in immune cell infiltration between the high and low STAT3 groups. (**H**) The correlation between immune cell infiltration and STAT3 expression. (**I**) Visualization of cell clustering based on UMAP algorithm. (**J**) The expression distribution of PRKCQ-AS1 and STAT3. (**K**) Expression changes of PRKCQ-AS1 in psoriasis lesions in different cells. *: P < 0.05, **: P < 0.01, ***: P < 0.001, ****P < 0.0001.

enriched in the high STAT3 expression group (Figure 9E,F and Table S3). Immunoinfiltration analysis results showed that the differences in CD4$^+$T cell infiltration patterns between the high and low STAT3 expression groups were very similar to those between the high and low PRKCQ-AS1 expression groups (Figure 9G), and the correlation was also similar (Figure 9H). These results support the role of PRKCQ-AS1 on STAT3.

We checked the expression of PRKCQ-AS1 and STAT3 in a large integrated single-cell sequencing dataset of psoriasis, and found co-expression in lymphocytes (Figure 9I and J), further confirming the role of PRKCQ-AS1 on STAT3. We examined the expression of PRKCQ-AS1 separately and found that its upregulation was mainly present in keratinocytes, with upregulation also observed in lymphocytes (Figure 9K). Combined with the previous results, this suggests that keratinocytes may be the source of PRKCQ-AS1 and regulate CD4$^+$T cells through exosomes.

Establishment of a Psoriatic Keratinocyte Model (HaCaT-Psoriasis)

To validate the conclusions drawn from our multi-omics data analysis, we conducted a series of cell experiments. The establishment of a psoriatic keratinocyte model was a crucial step in this process. We examined HaCaT cells processed according to existing modeling methods using qRT-PCR, and the results showed significant expression differences in

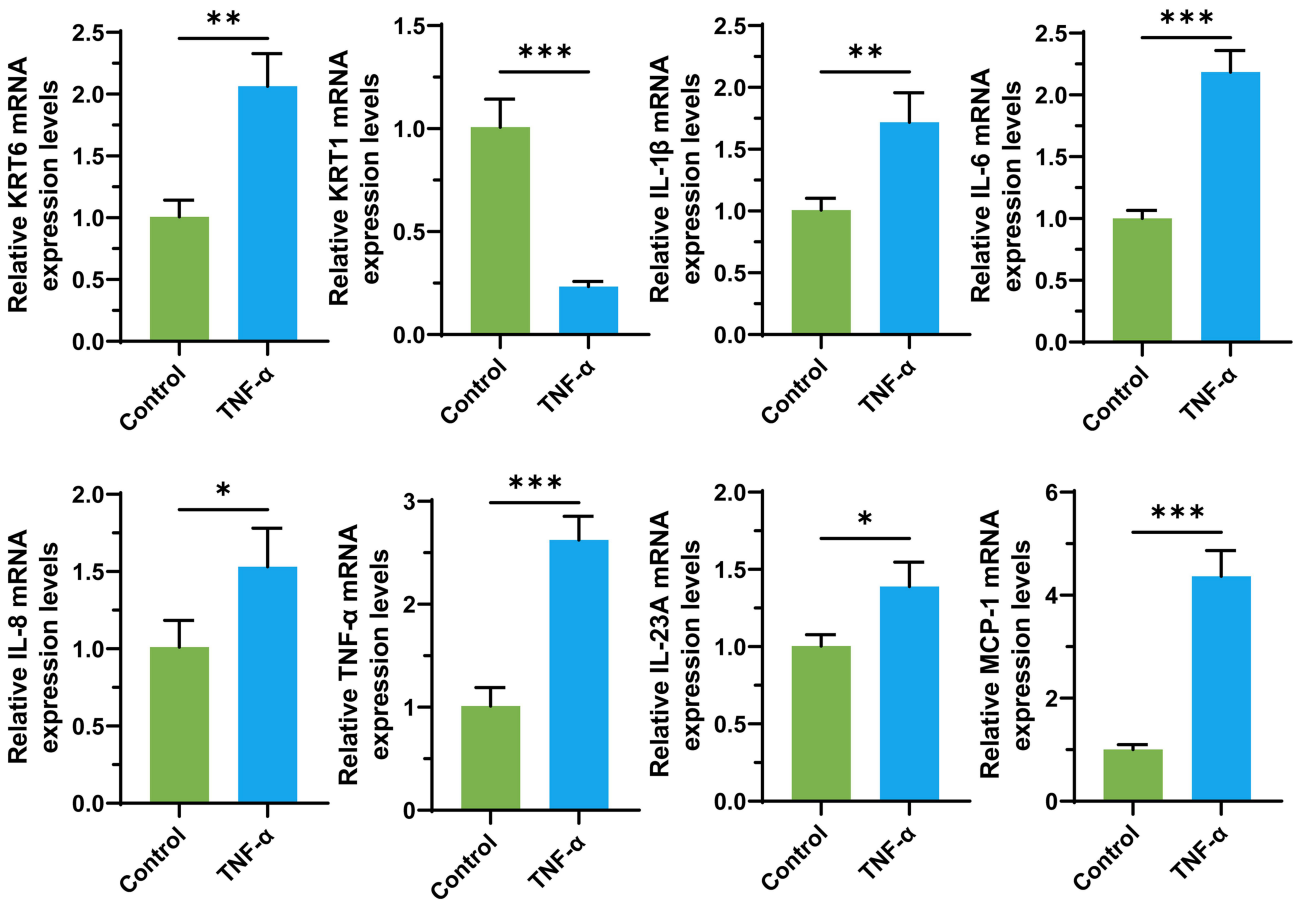

Figure 10 Validation of psoriasis keratinocyte model constructed by HaCaT cells and TNF-α. This figure shows the differential expression of multiple psoriasis keratinocyte markers at transcriptional levels between model group cells and control group cells. *: P < 0.05, **: P < 0.01, ***: P < 0.001.

several biomarkers between the TNF-α treated model group and the control group (Figure 10), consistent with the characteristics of psoriatic keratinocytes, proving the success of modeling.

HaCaT-Psoriasis Cells Can Enhance the Level of PRKCQ-AS1, Promote Th17 Differentiation and IL-17 secretion in $CD4^+$T Cells via Exosomes

We first need to verify the regulatory effect of psoriatic keratinocytes on $CD4^+$T cells. Immunofluorescence results showed that $CD4^+$T cells co-cultured with HaCaT-psoriasis cells differentiated more into Th17 compared to those co-cultured with control HaCaT cells, but this effect could be partially reversed by the use of the exosome inhibitor GW4869 (Figure 11A). qRT-PCR and ELISA results showed that $CD4^+$T cells co-cultured with HaCaT-psoriasis cells had higher levels of PRKCQ-AS1, TNF-α and IL-17, which could also be partially reversed by the use of GW4869 (Figure 11B and C). These results support that psoriatic keratinocytes upregulate the level of PRKCQ-AS1 in $CD4^+$T cells through exosomes, promoting Th17 differentiation and IL-17 secretion.

HaCaT Cells Can Transfer Upregulated PRKCQ-AS1 to $CD4^+$T Cells via Exosomes

To clarify the reason for the upregulation of PRKCQ-AS1 level in $CD4^+$T cells after co-culture, we overexpressed PRKCQ-AS1 in HaCaT cells through lentiviral transfection (Figure 11D) and conducted co-culture experiments. qRT-PCR results showed that $CD4^+$T cells co-cultured with PRKCQ-AS1-overexpressed HaCaT cells had significantly higher levels of PRKCQ-AS1 (Figure 11E). The results of directly incubating $CD4^+$T cells with extracted exosomes were consistent, as exosomes derived from PRKCQ-AS1-overexpressed HaCaT cells also significantly upregulated the level of PRKCQ-AS1 in $CD4^+$T cells (Figure 11F). These results indicate that HaCaT cells can transfer PRKCQ-AS1 to

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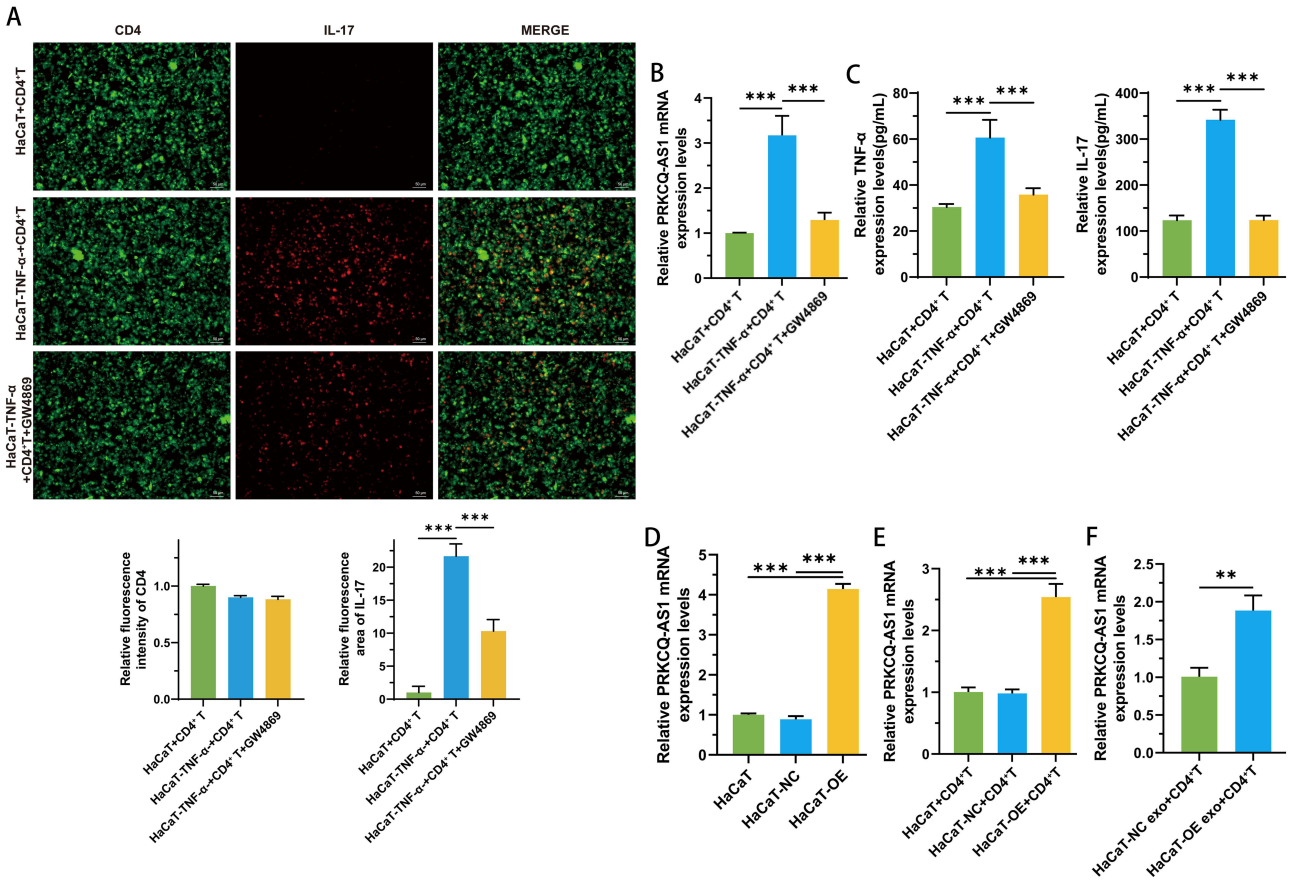

Figure 11 Upregulated PRKCQ-AS1 in HaCaT cells can upregulate the level of PRKCQ-AS1 in $CD4^+$T cells through exosomes, promoting Th17 cells differentiation and IL-17 secretion. (**A**) Detection of CD4 and IL-17 signals in $CD4^+$T cells after co-culture using immunofluorescence. There was no significant difference in CD4 signals (used as a reference for cell count) between groups, but IL-17 signals in $CD4^+$T cells co-cultured with HaCaT-psoriasis cells were significantly stronger than those in the control HaCaT cell co-culture group or the GW4869-treated group. (**B**) Detection of PRKCQ-AS1 level in $CD4^+$T cells after co-cultured with HaCaT-psoriasis cells by qRT-PCR. (**C**) Detection of TNF-α and IL-17 levels in $CD4^+$T cells after co-cultured with HaCaT-psoriasis cells by ELISA. (**D**) Validation of PRKCQ-AS1 overexpression in HaCaT cells by qRT-PCR. (**E**) Detection of PRKCQ-AS1 level in $CD4^+$T cells after co-cultured with PRKCQ-AS1-overexpressed HaCaT cells by qRT-PCR. (**F**) Detection of PRKCQ-AS1 level in $CD4^+$T after incubated with extracted exosomes from PRKCQ-AS1-overexpressed HaCaT cells by qRT-PCR. **: $P < 0.01$, ***: $P < 0.001$.

$CD4^+$T cells via exosomes, supporting that the upregulation of PRKCQ-AS1 in $CD4^+$T cells can be attributed to the transfer of upregulated PRKCQ-AS1 from psoriatic keratinocytes via exosomes.

PRKCQ-AS1 Can Promote Th17 Differentiation and IL-17 secretion in $CD4^+$T Cells

To confirm the attribution of increased Th17 differentiation and IL-17 secretion after co-culture, we directly overexpressed PRKCQ-AS1 in $CD4^+$T cells and conducted a series of assays. Immunofluorescence results showed that Th17 cell differentiation was significantly higher in PRKCQ-AS1-overexpressed $CD4^+$T cells compared to control $CD4^+$T cells (Figure 12A). ELISA results showed that the supernatant of PRKCQ-AS1-overexpressed $CD4^+$T cells contained more TNF-α and IL-17 (Figure 12B). These results suggest that PRKCQ-AS1 can promote Th17 differentiation and IL-17 secretion. We further examined the expression of IL-6/STAT3 signaling pathway markers by Western blot, and the results showed that the expression of IL-6 and the p-STAT3/STAT3 ratio were significantly higher in PRKCQ-AS1-overexpressed $CD4^+$T cells compared to the control group (Figure 12C), reflecting the activation state of the IL-6/STAT3 pathway, supporting the role of PRKCQ-AS1 through the STAT3 signaling pathway.

Discussion

Psoriasis is a chronic inflammatory skin disease primarily driven by immune system dysregulation. Studies have confirmed that the onset of psoriasis involves abnormal activation and dysfunction of various immune cells, including

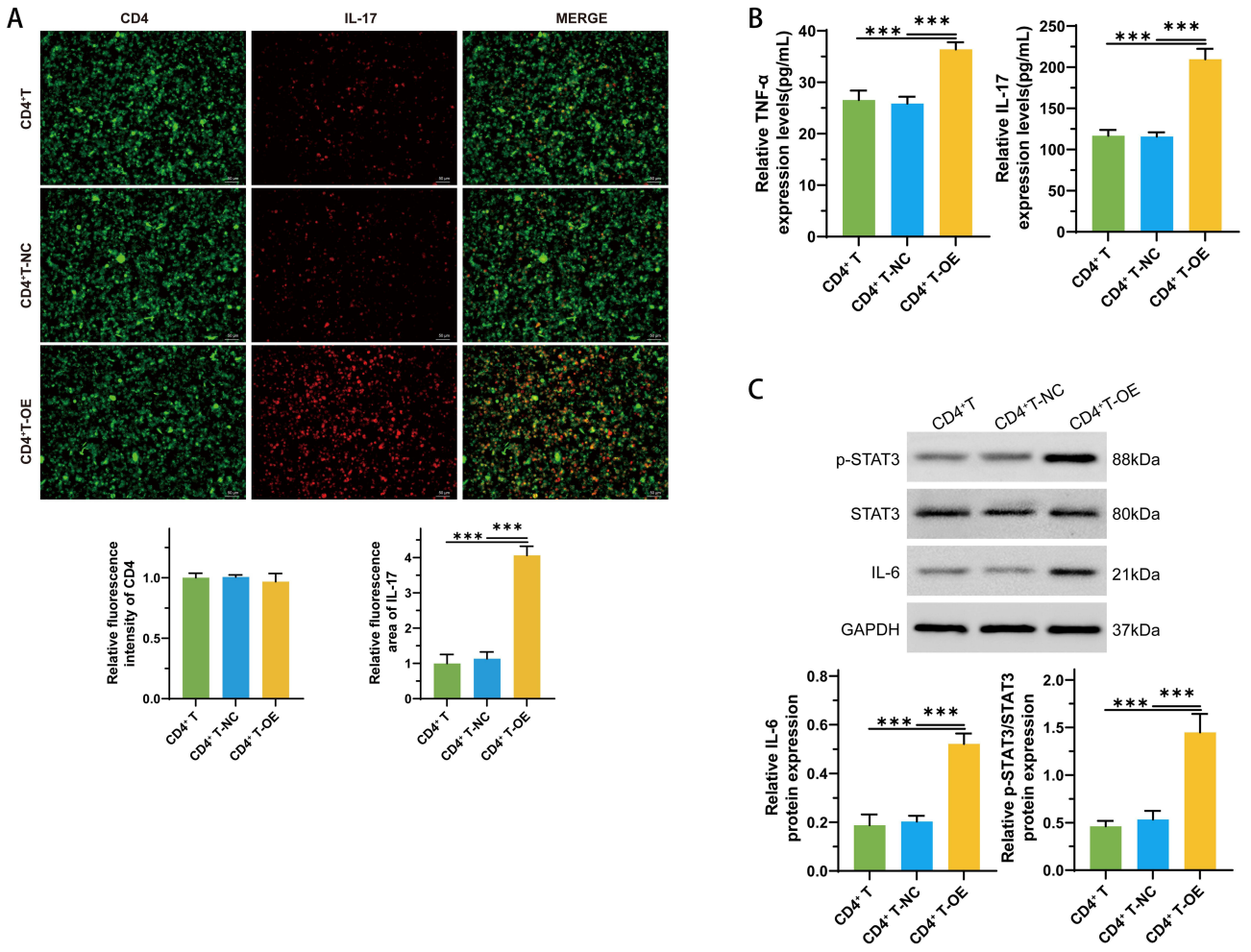

Figure 12 PRKCQ-AS1 may promote Th17 cell differentiation and IL-17 secretion through the STAT3 signaling pathway. (**A**) Detection of CD4 and IL-17 signals in $CD4^+$T cells after overexpression of PRKCQ-AS1 using immunofluorescence. There was no significant difference in CD4 signals (as a reference for cell count) between groups, but IL-17 signals in PRKCQ-AS1-overexpressed $CD4^+$T cells were significantly stronger than $CD4^+$T cells transfected with control plasmid or $CD4^+$T cells without transfection operation. (**B**) Detection of TNF-α and IL-17 levels in the supernatant of $CD4^+$T cell culture medium after transfection. (**C**) Detection of markers reflecting IL-6/STAT3 signaling pathway activation through Western blot after transfection. ***: $P < 0.001$.

macrophages, neutrophils, and T cells. Among them, the immune imbalance of $CD4^+$T cell subsets is one of the important markers of psoriasis, especially Th17 cells, whose secretion of IL-17 plays a central role in the pathogenesis of psoriasis.[7] Currently, targeted therapy against IL-17 has become a new strategy for the treatment of psoriasis, with marketed drugs such as secukinumab and ixekizumab showing good efficacy in treating moderate to severe plaque psoriasis. Furthermore, drugs targeting upstream IL-23 or downstream molecular pathways of IL-17 have also entered clinical use, highlighting the importance of IL-17[13]. However, current psoriasis treatments targeting a single inflammatory factor systemically have certain limitations, such as increasing the risk of systemic infections and tumors.[14] Therefore, in-depth research on the differentiation of Th17 cells and the secretion mechanisms of inflammatory factors such as IL-17 in psoriasis lesions is of great significance for revealing the pathogenesis of psoriasis and finding new therapeutic targets.

Exosomes are extracellular vesicles with a diameter of 30–150nm that can carry various signaling molecules to mediate intercellular communication. At present, research on the mechanisms of exosomes in psoriasis is limited, but existing studies have shown the correlation between exosomes and psoriasis. A study using chip technology analyzed miRNA expression in circulating exosomes from patients with psoriatic arthritis, plaque psoriasis, rheumatoid arthritis, and gouty arthritis, finding significant differential expression of five miRNAs: hsa-miR-151a-3p, hsa-miR-199a-5p, hsa-

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miR-370-3p, hsa-miR-589-5p, and hsa-miR-769-5p, which may be related to immune dysregulation.[21] This suggests that exosomes may play a role in the pathogenesis of psoriasis, potentially through the abnormal ncRNA they carry.

Do exosomes and their ncRNA participate in the regulation of Th17 cell differentiation and IL-17 secretion in psoriasis lesions? Currently, there is little research answering this question, possibly because the available exosome transcriptome sequencing data is very limited, greatly increasing the difficulty of exploring this issue.

After performing data quality control and batch effect correction on psoriasis bulk RNA sequencing data, we adopted a sophisticated method to explore the association between exosomes and ncRNAs, indirectly identifying key ncRNAs within exosomes. Specifically, we referred to the methods of Peng W. et al[27] to construct an exosome characterization (PEXS) in psoriasis bulk RNA sequencing data as a quantitative indicator of exosome behavior. To ensure the validity of this indicator, we conducted GSEA, correlation analysis, and other evaluations, which showed that this indicator could reflect exosome behavior in samples to a certain extent. Furthermore, our analysis demonstrated significant differences in PEXS between non-lesional and lesional psoriasis, and a large number of ncRNAs were correlated with PEXS, supporting the important role of exosomes in psoriasis and their potential function through ncRNAs. The results of immune infiltration analysis also supported the correlation between PEXS and the infiltration of multiple immune cells. In summary, these results provide a foundation for further investigation into ncRNAs that regulate Th17 cell differentiation and IL-17 secretion via exosomes.

Next, we investigated ncRNAs closely associated with PEXS using WGCNA. As the results showed, these 10 selected ncRNAs had significant expression correlations with 4 typical exosome markers and at least 87 pairs of correlations with the 119 exosome-related genes used to construct PEXS. These results demonstrated the relationship between the selected ncRNAs and exosomes. Additionally, results showed significant expression differences (P-adjusted<0.05) between non-lesional and lesional samples in both the integrated dataset and subsets for these 10 ncRNAs, suggesting their potential role in psoriasis.

Of course, the above results do not represent the value of these closely-exosome-related ncRNAs to psoriasis. Therefore, we further constructed machine learning diagnosis models. On one hand, this can reflect the value of these ncRNAs in psoriasis by exploring their performance in distinguishing non-lesional and lesional samples in psoriasis datasets. On the other hand, by analyzing the importance of variables in reliable diagnosis models, we can further screen for ncRNAs that contribute significantly to distinguishing psoriasis lesions, which may also be important ncRNAs in the pathogenesis of psoriasis. For the binary classification task in this study, we considered multiple factors when selecting machine learning algorithms.[42] In brief, compared with deep learning, traditional machine learning approaches typically do not involve an excessive number of network layers or complex hyperparameters, thereby reducing the risk of overfitting; furthermore, for simple data types and binary classification tasks, they achieve satisfactory performance while requiring fewer computational resources and less training data. Thus, we ultimately prefer traditional machine learning algorithms. Among the available traditional machine learning algorithms, we finally selected five methods according to our research objectives given that extensive literature and empirical case studies substantiate their advantages in classification tasks and feature selection. The LASSO regression model employs L1 regularization to select a subset of predictors that minimizes prediction error, thereby constructing an accurate and parsimonious model. RF leverages a parallel ensembling technique to concurrently fit multiple decision trees, effectively reducing overfitting and enhancing predictive accuracy. GBM, LightGBM, and XGBoost each utilize distinct gradient optimization strategies to minimize the loss function, which significantly mitigates overfitting and improves overall model performance. Additionally, these five algorithms incorporate both linear and nonlinear paradigms, facilitating a multifaceted evaluation of feature selection and classification performance, while minimizing the random effects associated with reliance on a single model, thereby enhancing the stability and generalizability of the results.

As shown in our results, we constructed five high-performance models using five machine learning algorithms. The performance of these five models across two independent test sets demonstrates their stability, with no apparent signs of overfitting. These findings support the value of ncRNAs which act as the model variables in psoriasis. To more accurately evaluate the contribution of each feature to the models and minimize biases in feature importance assessments across different models, we standardized the measurement by adopting “permutation cost” as the evaluation metric. Among the five models, PRKCQ-AS1, ZC3H12A-DT, and SH3PXD2A-AS1 consistently ranked in the top three in terms of

importance. This high level of consistency not only demonstrates the critical roles of these three ncRNAs in psoriasis but also suggests that biases potentially introduced by discrepancies in feature importance across models are no longer a major concern.

SH3PXD2A-AS1 can promote the proliferation of keratinocytes through the STAT3/SH3PXD2A-AS1/miR-125b/STAT3 positive feedback loop, thereby promoting the progression of psoriasis.[43,44] ZC3H12A-DT is an epithelial gatekeeper in normal epithelial cells.[45] Related studies have also reported the upregulation of PRKCQ-AS1 expression in psoriasis lesions and HaCaT cell psoriasis models.[46] These existing researches support the accuracy of our machine learning results and demonstrate the value of these three ncRNAs in psoriasis. However, no studies have yet explored whether and how they promote the progression of psoriasis through exosomes. Among them, PRKCQ-AS1 is of the greatest interest to us based on the evidence chain from multi-omics data we have obtained.

Before further exploring the role of PRKCQ-AS1, we first need to clarify the causal relationship between PRKCQ-AS1 expression and psoriasis. If the upregulation of PRKCQ-AS1 in psoriasis lesions is merely a result of the disease, then intervening in PRKCQ-AS1 for psoriasis treatment would be meaningless, and PRKCQ-AS1 is unlikely to be the upstream target regulating the Th17/IL-17 axis we are looking for. However, MR results based on genomic data indicate a causal relationship between PRKCQ-AS1 and psoriasis, with PRKCQ-AS1 expression being a risk factor for psoriasis. This alleviates our concerns and supports the significance of further exploring the mechanism of PRKCQ-AS1.

Analysis results of bulk RNA sequencing data indicate that PRKCQ-AS1 expression affects $CD4^+$T cell infiltration patterns and is positively correlated with Th17 cell differentiation and IL-17 secretion. Combined with MR results, we have reason to suspect that PRKCQ-AS1 can promote Th17 cell differentiation and IL-17 secretion.

How is PRKCQ-AS1 related to exosomes?

Based on the expression data of PRKCQ-AS1 from single-cell RNA sequencing data, we found that the upregulation of PRKCQ-AS1 in psoriasis is mainly concentrated in keratinocytes, with significant upregulation also observed in lymphocytes. The contents of exosomes are not only important molecules for their biological functions but also markers reflecting the state of their parent cells. Combining existing studies that have confirmed the upregulation of PRKCQ-AS1 expression in psoriasis lesions and HaCaT cell psoriasis models,[46] we speculate that keratinocytes are an important source of PRKCQ-AS1 which can act on $CD4^+$T cells via exosome transmission. Existing studies support our hypothesis. Exosomes can be secreted by keratinocytes and act on surrounding cells, such as melanocytes and immune cells. Studies have found that keratinocytes can regulate the expression and activity of melanosomal proteins through exosomes, thereby promoting melanin synthesis.[47] Additionally, exosomes derived from keratinocytes can activate neutrophils, exacerbating skin inflammatory responses.[48] As an important component of the immune system, T cells can also receive exosomes released by other cells, thereby affecting their function. For example, exosomes derived from macrophages can regulate the balance of Treg/Th17 cells.[49] In the pathogenesis of psoriasis, T cells can recognize exosomes transmitted by mast cells.[50] Studies have confirmed the interaction between T cells and keratinocytes.[51] These researches and our data support that PRKCQ-AS1 may originate from keratinocytes and regulate $CD4^+$T cell function through exosomes.

How does PRKCQ-AS1 promote Th17 cell differentiation and IL-17 secretion in $CD4^+$T cells?

Analysis results of bulk RNA sequencing data showed the association of PRKCQ-AS1 expression with STAT3 signaling pathway markers and gene sets. The impact of their expression on the enrichment results of Th17 cell differentiation-related pathways showed consistency. We also observed the co-expression of PRKCQ-AS1 and STAT3 in lymphocytes in single-cell RNA sequencing data. Additionally, existing studies have reported the activation of the STAT3 signaling pathway by PRKCQ-AS1 in liver cancer cells.[35] Considering that STAT3 activation in $CD4^+$T cells is an important supporting factor for Th17 cell differentiation and IL-17 secretion,[52] we have sufficient reason to suspect that PRKCQ-AS1 promotes Th17 cell differentiation and IL-17 secretion through STAT3 in $CD4^+$T cells in psoriasis lesions.

In summary, based on existing researches and multi-omics data, we discovered through various bioinformatics and machine learning methods that the overexpression of PRKCQ-AS1 in psoriasis keratinocytes is likely to activate the STAT3 signaling pathway in $CD4^+$T cells via exosomes, promoting Th17 cell differentiation and IL-17 secretion, thereby forming an inflammatory loop that advances psoriasis progression (Figure 13).

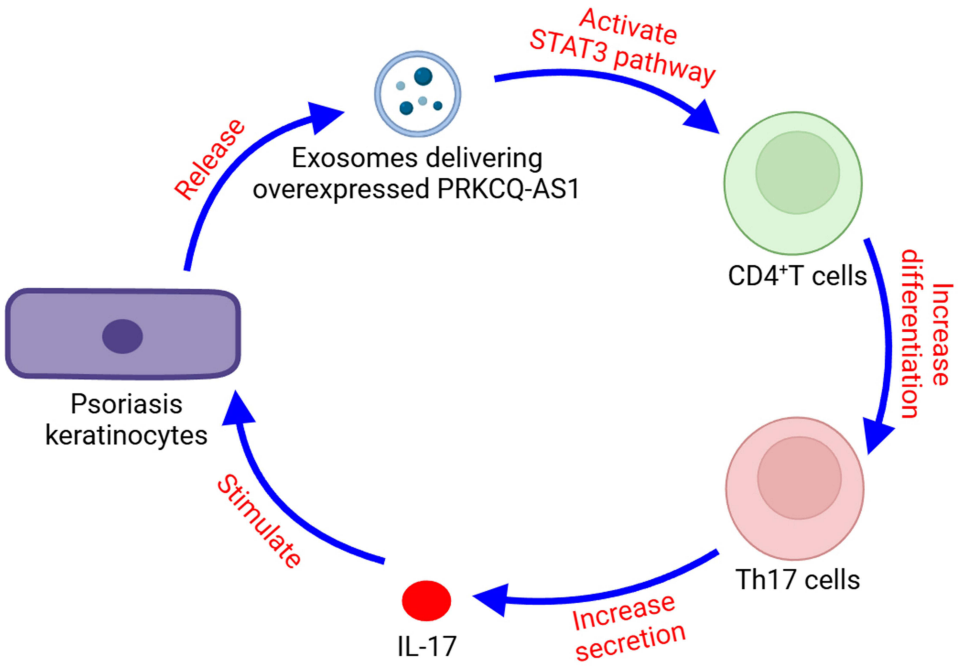

Figure 13 The inflammatory loop of PRKCQ-AS1 in psoriasis.

We conducted an extensive literature review to elucidate the significance of our findings. Regarding PRKCQ-AS1, its overexpression in psoriasis lesions and in the HaCaT cell model of psoriasis has been well-documented.[46] Additionally, PRKCQ-AS1 has been implicated in neuroblastoma tumorigenesis,[53] colorectal cancer cell proliferation and migration,[54] and prognostic outcomes in diffuse large B-cell lymphoma.[55] These studies underscore the functional diversity and significance of PRKCQ-AS1 across various diseases, suggesting its potentially pivotal role in psoriasis. However, no study to date has investigated the regulation of $CD4^+$T cells by PRKCQ-AS1 in psoriasis. With regard to exosomal lncRNAs, studies have demonstrated their role in regulating $CD4^+$T cell function or contributing to psoriasis pathogenesis. For example, studies have shown that tumor-derived exosomes promote Th17 cell differentiation in colorectal cancer by transferring lncRNA CRNDE-h,[18] while exosomal lncRNA TUG1 from bone marrow mesenchymal stem cells modulates the Th17/Treg balance via BLIMP1.[56] Moreover, certain exosomal lncRNAs have been proposed as diagnostic and prognostic biomarkers for autoimmune diseases, including psoriasis.[57] These findings suggest that exosomal lncRNAs could contribute to psoriasis progression by influencing Th17 cells. Nonetheless, both the association between PRKCQ-AS1 and exosomes and the role of these exosomes in regulating CD4+T cell function remain poorly understood in psoriasis. Notably, studies have indicated that in hepatocellular carcinoma cells, PRKCQ-AS1 activates the STAT3 signaling pathway through the miR-143-3p/IL-6/STAT3 axis,[35] and because STAT3 activation is crucial for the differentiation of $CD4^+$T cells into Th17 cells,[52] these results are highly consistent with our observations. Therefore, our evidence from multi-omics data strongly suggest that keratinocyte-derived exosomal PRKCQ-AS1 may promote psoriasis progression by activating STAT3, thereby facilitating Th17 cell differentiation and IL-17 secretion. If supported by experimental evidence, these findings will enhance our understanding of the role of PRKCQ-AS1 in regulating $CD4^+$T cells in psoriasis and update our insights into the function of exosomal lncRNA in psoriasis pathogenesis.

In our conclusions based on evidence from multi-omics data, the pro-inflammatory effects of Th17 cell differentiation and IL-17 secretion on keratinocytes have been widely discussed and proven, and the upregulation of PRKCQ-AS1 expression in psoriasis lesions and HaCaT cell psoriasis models has also been confirmed as discussed above. Our experiments only need to focus on proving: (1) Psoriasis keratinocytes can promote Th17 cell differentiation and IL-17 secretion via exosomes; (2) Psoriasis keratinocytes can upregulate PRKCQ-AS1 levels in $CD4^+$T cells via exosomes; (3) PRKCQ-AS1 in $CD4^+$T cells can promote Th17 cell differentiation and IL-17 secretion, and this effect is achieved

through the activation of the STAT3 signaling pathway. The results of the cell experiments are consistent with the conclusions obtained from multi-omics data, supporting our viewpoint.

All in all, we have revealed that PRKCQ-AS1 derived from psoriasis keratinocytes can activate the STAT3 signaling pathway in $CD4^+$T cells via exosomes, promoting Th17 cell differentiation and IL-17 secretion. On one hand, our research has refined the mechanism of PRKCQ-AS1 in psoriasis. On the other hand, we provided specific example of exosome-related regulation of $CD4^+$T cells in psoriasis.

Furthermore, considering the regional location of keratinocytes, if this regulatory mechanism is unique to skin tissues in Th17/IL-17-mediated diseases, this study will provide a highly tissue-selective therapeutic theoretical basis for inhibiting IL-17 in related skin diseases, thereby avoiding the systemic tumor and infection risks associated with systemic IL-17 inhibitors theoretically.[14] Additionally, research has highlighted the potential benefits of targeting upstream pathways of IL-17 rather than directly addressing IL-17 itself. By avoiding interference with IL-17 secretion from non-Th17 cells, such an approach may reduce immune suppression in non-lesional areas.[58] Therefore, based on the mechanism identified in our study, keratinocyte-derived exosomal PRKCQ-AS1 emerges as a potential therapeutic target with substantial research opportunities and considerable clinical relevance. Future studies could explore the therapeutic potential of the mechanism identified in our research, either by targeting PRKCQ-AS1 or employing strategies centered on keratinocyte-derived exosomes.

Inevitably, our study has some limitations. During the integration of three bulk RNA-seq datasets, limitations in the original data restricted our ability to control confounding variables beyond the accessible data, such as disease severity and treatment history, which may further impact the generalizability of the conclusions. Moreover, the exploration of the mechanism by which PRKCQ-AS1 promotes Th17 cell differentiation and IL-17 secretion is not complete, and our multi-omics data analysis and cell experiments cannot yet clarify the extent to which PRKCQ-AS1's effect depends on STAT3 activation or the precise mechanism by which PRKCQ-AS1 activates STAT3. Additionally, due to current constraints, this study has not yet been able to verify the mechanism in vivo. Furthermore, based on our present data, we are unable to evaluate the off-target effects of PRKCQ-AS1 as a therapeutic target, which could potentially influence its clinical value. Of course, the above limitations do not affect the reliability of the conclusions. We will refine our work in the next phase and further explore effective and highly tissue-selective therapeutic targets for psoriasis that can block this inflammatory loop.

Conclusion

In this study, we uncovered that PRKCQ-AS1 is an important lncRNA in the exosomes from keratinocytes in psoriasis. Exosomal PRKCQ-AS1 from psoriatic keratinocytes can trigger the STAT3 signaling pathway in $CD4^+$T cells, which in turn facilitates the differentiation of Th17 cells and the release of IL-17, thereby forming a complete inflammatory loop and promoting the progression of psoriasis. Our findings have perfected the role of PRKCQ-AS1 in psoriasis, providing evidence for the regulation of $CD4^+$T cells by exosomes and the promotion of Th17 cell differentiation and IL-17 secretion, offering potential therapeutic targets and ideas for psoriasis.

Abbreviations

GWAS, genome-wide association study; GSEA, gene set enrichment analysis; miRNA, microRNA; lncRNA, long non-coding RNA; WGCNA, weighted gene co-expression network analysis; NCBI, National Center for Biotechnology Information; GEO, Gene Expression Omnibus; NN, normal skin tissue from normal samples; PN, normal skin tissue from patients with psoriasis; PP, psoriasis lesions from patients with psoriasis; eQTL, expression Quantitative Trait Loci; IEU, Integrative Epidemiology Unit; SNPs, Single Nucleotide Polymorphisms; PCA, principal component analysis; PEXS, exosome-related PCA scores; GS, Gene Significance; MM, Module Membership; LASSO, Least Absolute Shrinkage and Selection Operator; XGBoost, eXtreme Gradient Boosting; RF, Random Forest; GBM, Gradient Boosting Machine; LGBM, Light Gradient Boosting Machine; ROC, Receiver Operating Characteristic; AUC, Area Under the Curve; SHAP, SHapley Additive exPlanations; MR, Mendelian randomization; IVs, instrumental variables; IVW, Inverse Variance Weighting; HaCat, immortalized human keratinocytes; PBS, phosphate-buffered saline; qRT-PCR, quantitative real-time polymerase chain reaction; TBST, Tris-buffered saline containing

Tween-20; BCA, bicinchoninic acid assay; PVDF, polyvinylidene fluoride; BP, biological processes; CC, cellular components.

Data Sharing Statement

The publicly available data used in this study can be downloaded from the designated addresses, with details provided in the methods section. Our code and data can be obtained by contacting the corresponding author upon reasonable request.

Ethics Approval

The research project has undergone ethical review by the Nanfang College Academic Ethics Committee (No. NF2025040701). The committee confirms that this study solely involves public database data and cell lines, which complies with established ethical norms and standards.

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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.

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Disclosure

The authors report no conflicts of interest in this work.

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