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Original Article

Single-cell transcriptomics and machine learning identify SQLE as a candidate lipid metabolism gene associated with keratinocyte-Th17 cell crosstalk in obesity-exacerbated psoriasis

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Abstract: Background: Psoriasis is a systemic, immune-mediated inflammatory skin disease strongly associated with metabolic syndrome and obesity. While dysregulation of systemic lipid metabolism is a known exacerbating factor, the localized metabolic reprogramming within the skin microenvironment and its specific role in driving intercellular crosstalk between structural and immune cells remain largely unknown. Methods: We integrated single-cell RNA sequencing (scRNA-seq) of psoriatic and normal skin with bulk transcriptomic data. Lipid metabolic activity at the single-cell level was evaluated using AUCell. To identify diagnostic hub genes, three machine learning algorithms - LASSO regression, Random Forest (RF), and Boruta - were applied to the bulk dataset. T cell subpopulation heterogeneity and intercellular communication were assessed using Seurat and CellChat. To provide preliminary validation of our bioinformatics findings in vivo, we established an obese-psoriasis mouse model using a High-Fat Diet (HFD) combined with topical Imiquimod (IMQ), evaluated via histological staining, immunohistochemistry (IHC), immunofluorescence and ELISA. Results: ScRNA-seq analysis characterized 8 major skin cell types, revealing a significant expansion of T cells and myeloid cells in psoriatic lesions. AUCell scoring demonstrated that psoriatic keratinocytes exhibited the highest lipid metabolic activity among all cell types, with a significant elevation compared to normal controls. Machine learning on bulk transcriptomics identified four core lipid metabolism genes (*SQLE*, *SPTLC2*, *PLA2G4D*, and *PLBD1*). *SQLE* was significantly upregulated in psoriatic keratinocytes and demonstrated high diagnostic accuracy. The analysis of the cell communication network suggested potential communication relationships between $SQLE^+$ keratinocytes and Th17 cells, although the identified ligand-receptor pairs were not specific to Th17 cells. In vivo verification demonstrated that diet-induced obesity significantly exacerbated the psoriasis-like lesions induced by IMQ. Immunohistochemical results showed that high expression of SQLE was located in the keratinocytes area, and the infiltration of $CD4^+IL17A^+$ Th17 cells in the dermis increased. Additionally, in the obesity-psoriasis model, ELISA test results revealed that the levels of IL-17A and TNF-α were significantly elevated. Conclusion: Our findings identified SQLE as a candidate molecular link between keratinocyte lipid metabolic dysfunction and Th17 cell-mediated cutaneous inflammation in the context of obesity. Our findings suggest that the *SQLE*-Th17 pathway is potentially hyperactivated under obese conditions, contributing to psoriasis exacerbation. Targeting SQLE and its downstream metabolic-immune communication pathways represents a promising therapeutic frontier for psoriasis patients with comorbid metabolic syndrome, pending validation through functional studies.

Keywords: Psoriasis, obesity, SQLE, lipid metabolism, Th17 cell

Introduction

Psoriasis is a chronic, relapsing inflammatory skin disease driven jointly by genetic, immunological, and environmental factors, with a global prevalence of approximately 2%-3%. Its clinical manifestations include well-demarcated erythematous plaques and silvery-white scales. The main pathological features are keratinocyte hyperproliferation, abnormal differentiation, and massive infiltration of immune cells (especially T cells) in the dermis [1]. Although

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targeted therapies such as biologics have significantly improved the prognosis for patients with severe disease, the high recurrence rate, treatment resistance in some patients, and frequent metabolic comorbidities present substantial challenges for the precision treatment of psoriasis [2].

A large body of epidemiological evidence indicates that obesity, a globally prevalent metabolic disorder syndrome, is an independent risk factor for psoriasis. Obesity not only increases the risk of developing psoriasis but is also closely associated with lesion severity, prolonged disease course, and decreased treatment responsiveness [3]. Notably, while biologics targeting specific cytokines have greatly improved therapeutic outcomes, some patients continue to exhibit treatment resistance [4], and obesity is the most significant independent risk factor mediating this phenomenon [5]. In-depth studies suggest that lipid metabolism disorders in the epidermal microenvironment can remodel local immune responses, thereby driving biologic resistance in the context of obesity [6]. This suggests that elucidating the molecular link between lipid metabolism disorders and the psoriatic immune microenvironment may provide new insights for overcoming treatment resistance. Therefore, it is urgent to thoroughly elucidate the abnormal lipid profiles (including the accumulation of free cholesterol, triglycerides, and various phospholipids) [7] present in psoriatic lesions and serum, as well as the underlying key lipid metabolic enzymes and their pivotal roles in specific skin cells.

Squalene epoxidase (SQLE) is the second rate-limiting enzyme in the cholesterol biosynthesis pathway, catalyzing the epoxidation of squalene to 2,3-oxidosqualene [8]. Traditionally, SQLE has been thought to primarily participate in maintaining cell membrane cholesterol homeostasis, but recent studies have revealed its important non-classical immunomodulatory functions. In hepatocellular carcinoma, high SQLE expression can induce the generation of oxidized low-density lipoproteins, driving pro-tumoral macrophage polarization via the TREM2-SYK-CEBPα axis, which leads to $CD8^+$ T cell dysfunction and is closely related to immunotherapy resistance [9]. In pancreatic cancer, SQLE metabolically clears squalene, recruiting myeloid-derived suppressor cells and tumor-associated macrophages to promote tumor immune evasion [10]. Furthermore, in hepatocellular carcinoma (LIHC), multi-cohort and spatial transcriptomics studies have confirmed that high SQLE expression is significantly associated with reduced $CD8^+$ T cell infiltration and anti-tumor immunosuppression [11]. Systematic analyses based on multiple cancer types further indicate that SQLE expression is significantly correlated with the level of immune cell infiltration in disease states [12]. These studies collectively suggest that SQLE is not only a rate-limiting enzyme in cholesterol metabolism but also a key molecule broadly involved in immune regulation. However, its expression pattern, cellular localization, and immunopathological significance in psoriasis, a classical inflammatory skin disease, have not yet been systematically reported.

Based on preliminary single-cell RNA sequencing data, we constructed a single-cell atlas of psoriatic skin. Through the lipid metabolism gene set AUCell activity scoring, we found that keratinocytes are the most active cell population in lipid metabolism, and the lipid metabolism pathway is aberrantly activated in psoriasis. By further combining the GEO microarray database with three machine learning algorithms (LASSO, Random Forest and Boruta) for cross-screening, we identified SQLE as one of the core lipid metabolism genes associated with psoriasis, and SQLE is specifically highly expressed in the psoriatic keratinocyte subpopulation. Cell communication analysis suggested potential interaction networks between $SQLE^+$ keratinocytes and Th17 cells. Based on these bioinformatics findings, we hypothesized that the cholesterol synthesis reprogramming potentially driven by SQLE recruits circulating Th17 cells to infiltrate the lesions; simultaneously, it may further promote the secretion of IL-17A and TNF-α by Th17 cells, amplify the local inflammatory loop, and induce keratinocyte proliferation and neutrophil recruitment. This suggests that $SQLE^+$ keratinocytes may play a dual “metabolic-immune” role in psoriatic lesions, by participating in the remodeling of the Th17-dominated pro-inflammatory immune microenvironment. The above inferences imply that the SQLE expression level may serve as a potential biomarker for predicting biologic response and provide a new “dual metabolic-immune targeting” strategy for psoriasis patients with comorbid obesity/metabolic syndrome.

Nevertheless, the in vivo function, targeted cell interaction networks, and exact causal mechanisms of SQLE in psoriasis, especially in the complex pathological context of comorbid obesity, remain unexplored. Based on this, the present study proposes the hypothesis that obesity exacerbates psoriasis-like lesions by upregulating SQLE expression in epidermal keratinocytes, thereby activating the inflammatory communication loop between keratinocytes and Th17 cells. To explore this hypothesis, we first utilized single-cell transcriptomics and machine learning to screen SQLE as a key target. Subsequently, we established four groups of mouse models: a normal control group, a psoriasis-only group, an obesity-only group, and an obesity with psoriasis group. Combining immunohistochemistry and ELISA, we preliminarily analyzed the potential mechanisms of SQLE-mediated keratinocyte-Th17 cell interactions in obesity-exacerbated psoriasis from multiple dimensions, including histopathology, protein expression, and cell infiltration. The correlational evidence generated by this study may provide potential new insights for the precise intervention of obesity-combined psoriasis and offer experimental evidence and theoretical references for translational research on targeting key lipid metabolic enzymes in the treatment of psoriasis.

Methods

Acquisition and processing of scRNA-seq data

This study downloaded the scRNA-seq dataset of psoriatic lesions and healthy control skin tissues from the Gene Expression Omnibus (GEO) public database under the accession number GSE173706. The R package Seurat (v5) was used for the preprocessing and integration analysis of the single-cell transcriptome data. The cell quality control filtering criteria were as follows: retaining valid cells with the number of expressed genes between 200 and 5,000, total UMI counts between 200 and 30,000, mitochondrial gene expression ratio < 30%, and hemoglobin gene expression ratio < 5%. After normalizing the data for cells passing quality control, the top 2,000 highly variable genes were selected; based on the original sample source labels, the Harmony algorithm was applied to remove cross-sample technical batch effects, thereby completing data integration.

Unsupervised clustering and cell type annotation

Principal Component Analysis (PCA) was performed on the normalized data, and the top 15 principal components were selected to construct a K-nearest neighbor graph. Subsequently, the Louvain algorithm was used for community detection (with the resolution parameter set to 1.0) to achieve cell clustering. For visualization, the UMAP algorithm was used to display the cell clustering results on a two-dimensional plane.

Based on classical cell type marker genes, manual annotation was performed for each cell cluster: keratinocytes (KRT1, KRT5, KRT10, KRT14), fibroblasts (DCN, CFD, COL1A2), T cells (CD3D, CD3E, TRAC, IL32), endothelial cells (PECAM1, CLDN5, TM4SF1), smooth muscle cells (MYL9, ACTA2, TAGLN), melanocytes (MLANA, PMEL, TYRP1), myeloid cells (AIF1, LYZ), mast cells (CTSG, CPA3, TPSAB1), sweat glands (SCGB2A2, SCGB1D2), and neural cells (PMP22, PLP1, MPZ). Before the analysis, the "org.Hs.eg.db" package was used to convert ENSEMBL gene IDs to gene symbols to unify gene identifiers for subsequent analysis and visualization.

Single-cell lipid metabolism activity scoring

The Reactome lipid metabolism pathway gene set REACTOME_METABOLISM_OF_LIPIDS was downloaded from the MSigDB database. The AUCell package was used to calculate the Area Under the Curve (AUC) score of this pathway for each cell, serving as the lipid metabolism activity score. Based on the median lipid metabolism activity score, cells were divided into a high activity group (High) and a low activity group (Low). Seurat's "FindMarkers" function was utilized with the Wilcoxon rank-sum test to identify differentially expressed genes between the two groups.

Bulk transcriptome data and machine learning to screen core genes

The psoriasis gene expression microarray dataset GSE30999 was downloaded from the GEO database. Based on the AUCell lipid metabolism activity scores of the single-cell transcriptome data, genes highly correlated with the lipid metabolism score were screened via Spearman correlation analysis. Subsequently,

three machine learning algorithms were employed in the GSE30999 cohort to screen for core diagnostic genes: LASSO regression: Using the "glmnet" package, non-zero coefficient feature genes corresponding to "lambda.min" were selected through 10-fold cross-validation; Random Forest: Using the "randomForest" package (number of decision trees ntree = 2000), the top 15 key genes were selected based on the MeanDecreaseGini; Boruta algorithm: Using the "Boruta" package (maximum iterations maxRuns = 500) for robust feature selection. Finally, the intersection of the genes identified by the three algorithms was defined as the core feature genes associated with lipid metabolism in psoriasis.

T cell subpopulation sub-clustering and cell-cell communication analysis

The T cell population was extracted from the overall Seurat object for re-clustering. Subpopulations were annotated based on marker genes: $CD4^+$ T cells (CD4, IL7R), $CD8^+$ T cells (CD8A, CD8B), regulatory T cells (FOXP3, IL2RA), Th1 cells (IFNG, TNF), NK/T cells (GNLY, NKG7), Th2 cells (IL4, IL5, IL13), proliferating T cells (MKI67, TOP2A), and Th17 cells (IL17A, IL17F, RORC, IL22, CCR6). Keratinocytes were divided into $SQLE^+$ and $SQLE^-$ groups based on the SQLE expression level. Using the CellChat database and methodology, we calculated communication probabilities based on normalized ligand and receptor expression levels to construct a key signaling network between $SQLE^+$ keratinocytes and Th17 cells.

Experimental animals and model establishment

Six-week-old SPF male Balb/c mice were purchased from Shaanxi Shanyao Medical Biotechnology Co., Ltd. After 1 week of adaptive housing, they were randomly divided into a normal diet group (ND, fat energy ratio 10%) and a high-fat diet group (HFD, fat energy ratio 60%, Xietong Biology XTHF60). The HFD was pre-fed for 12 weeks to establish obesity and a state of obesity-associated metabolic milieu, aiming to simulate and investigate the "catalytic" effect of lipid metabolism disorders on psoriasis progression. Subsequent modeling interventions were performed once the body weight of the HFD group mice was significantly higher than that of the ND group.

Psoriasis-like skin lesion model construction

The backs of the mice were shaved (area 2 cm × 3 cm), and they were randomly divided into the following 4 groups (n = 6 per group): ND group (normal diet+topical Vaseline on the back); HFD group (high-fat diet+topical Vaseline on the back); ND+IMQ group (normal diet+topical imiquimod on the back); HFD+IMQ group (high-fat diet+topical imiquimod on the back). Except for the ND and HFD groups which received Vaseline, the other groups were topically applied with 62.5 mg of 5% imiquimod (IMQ) cream (Sichuan Mingxin Pharmaceutical Co., Ltd.) daily for 7 consecutive days. The erythema, scaling, and skin thickening of the lesions were scored daily (0-4 points for each item) according to the Psoriasis Area and Severity Index (PASI) standard.

Sample collection and histopathology

After the mice were sacrificed by cervical dislocation under deep isoflurane anesthesia (5% induction, maintained at 2-3% until respiratory arrest, followed by cervical dislocation to ensure death), blood, back skin lesions, and liver tissues were collected. A portion of the tissues was fixed in 4% paraformaldehyde, paraffin-embedded, and sectioned (thickness 4-5 μm). Hematoxylin-eosin (H&E) staining was performed to observe pathological morphology and measure epidermal thickness under a microscope.

Immunohistochemistry and multiplex immunofluorescence

IHC: Tissue sections were deparaffinized to water, subjected to antigen retrieval (microwave method, EDTA), and blocked for endogenous peroxidase. Primary antibody: anti-SQLE antibody (1:200, 12544-1-AP, Proteintech) was added dropwise and incubated overnight at 4°C in a humidified chamber. The next day, corresponding HRP-labeled secondary antibodies were applied, followed by color development using a DAB kit and nuclear counterstaining with hematoxylin. ImageJ software was used for semi-quantitative analysis.

mIF: After pre-treatment of the sections, anti-CD4 (1:3000, GB15064, Servicebio) and anti-IL-17A (1:2000, GB11110-1, Servicebio) antibodies were added and incubated overnight at 4°C. Subsequently, sections were incubated

with fluorophore-labeled secondary antibodies (S-vision Immunohistochemical Polymer Antibody, G1302) for 1 hour at room temperature in the dark and DAPI was used for nuclear counterstaining and mounting. Images were captured under a laser confocal microscope, and $CD4^+IL\text{-}17A^+$ double-positive cells in the dermis were defined as Th17 cells and counted.

Biochemical indicators and enzyme-linked immunosorbent assay (ELISA)

Serum triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were detected using a fully automated biochemical analyzer. After homogenizing the skin lesion tissues, we used ELISA kits to detect the concentrations of IL-17A (Solarbio sekm-0018) and TNF-α (Solarbio sekm-0034).

Statistical analysis

Experimental data were statistically analyzed using GraphPad Prism 9.0 software, and the results were expressed as Mean ± Standard Deviation (Mean ± SD). The comparison of means between two independent groups used a two-tailed unpaired t-test; comparisons among multiple groups used one-way analysis of variance (One-way ANOVA), and pairwise comparisons between groups used Tukey's multiple comparison test. $P < 0.05$ was considered statistically significant.

Results

Skin single-cell atlas reveals changes in the psoriatic immune microenvironment

After rigorous quality control and batch correction, single-cell data of psoriatic and normal skin samples were integrated to obtain a high-quality dataset. Unsupervised UMAP clustering initially divided the cells into 27 Seurat subpopulations (**Figure 1A**). Based on a panel of classical marker genes (**Figure 1B**), we accurately annotated the cells into 8 major types: keratinocytes, fibroblasts, T cells, endothelial cells, smooth muscle cells, melanocytes, myeloid cells, and neural cells (**Figure 1C**). In both states, keratinocytes constituted the vast majority of cells. Notably, the cell proportion analysis showed (**Figure 1D**, **1E**) that compared to normal control skin, the proportions of infiltrating T cells and myeloid cells were significantly increased in psoriatic lesions. This suggests a significant remodeling of the local immune microenvironment in psoriatic lesions.

Keratinocytes exhibit dominant lipid metabolism activity in psoriasis

Given the established clinical association between psoriasis and lipid metabolism disorders, we employed the AUCell algorithm to quantify single-cell lipid metabolism activity by calculating lipid metabolism-related gene (LMRG) scores. The UMAP feature plots showed that lipid metabolism activity was concentrated in a specific microenvironmental niche, predominantly within the keratinocyte population (**Figure 2A**, **2B**). Quantitative comparison revealed that the overall LMRG score in the psoriasis group was significantly higher than that in the control group (**Figure 2C**).

Additionally, significant metabolic heterogeneity was observed among different cell types. Keratinocytes exhibited the highest absolute LMRG scores among all cell types, which is consistent with their physiological role in epidermal barrier formation; importantly, these scores were further significantly upregulated in the psoriatic state compared to controls (**Figure 2D**). By dividing the cells into high and low metabolic state groups (**Figure 2E**), we performed differential expression analysis (**Figure 2F**) and Spearman correlation ranking (**Figure 2G**) to extract the core genes driving this hypermetabolic signature for subsequent feature screening.

Machine learning identifies SQLE as a core diagnostic lipid metabolism gene for psoriasis

To screen for the most robust diagnostic biomarkers from the lipid metabolism-related hub genes, we mapped the aforementioned gene signatures to the bulk RNA-seq dataset (GSE30999) and optimized feature selection through three different machine learning methods: LASSO regression screened a set of key features (**Figure 3A**, **3B**); Random Forest extracted the top 15 most important variables (including PLBD1, PLA2G4D, SPTLC2, and SQLE) (**Figure 3C**, **3D**); and the Boruta algorithm confirmed the significantly relevant features (**Figure 3E**). Taking the intersection of the

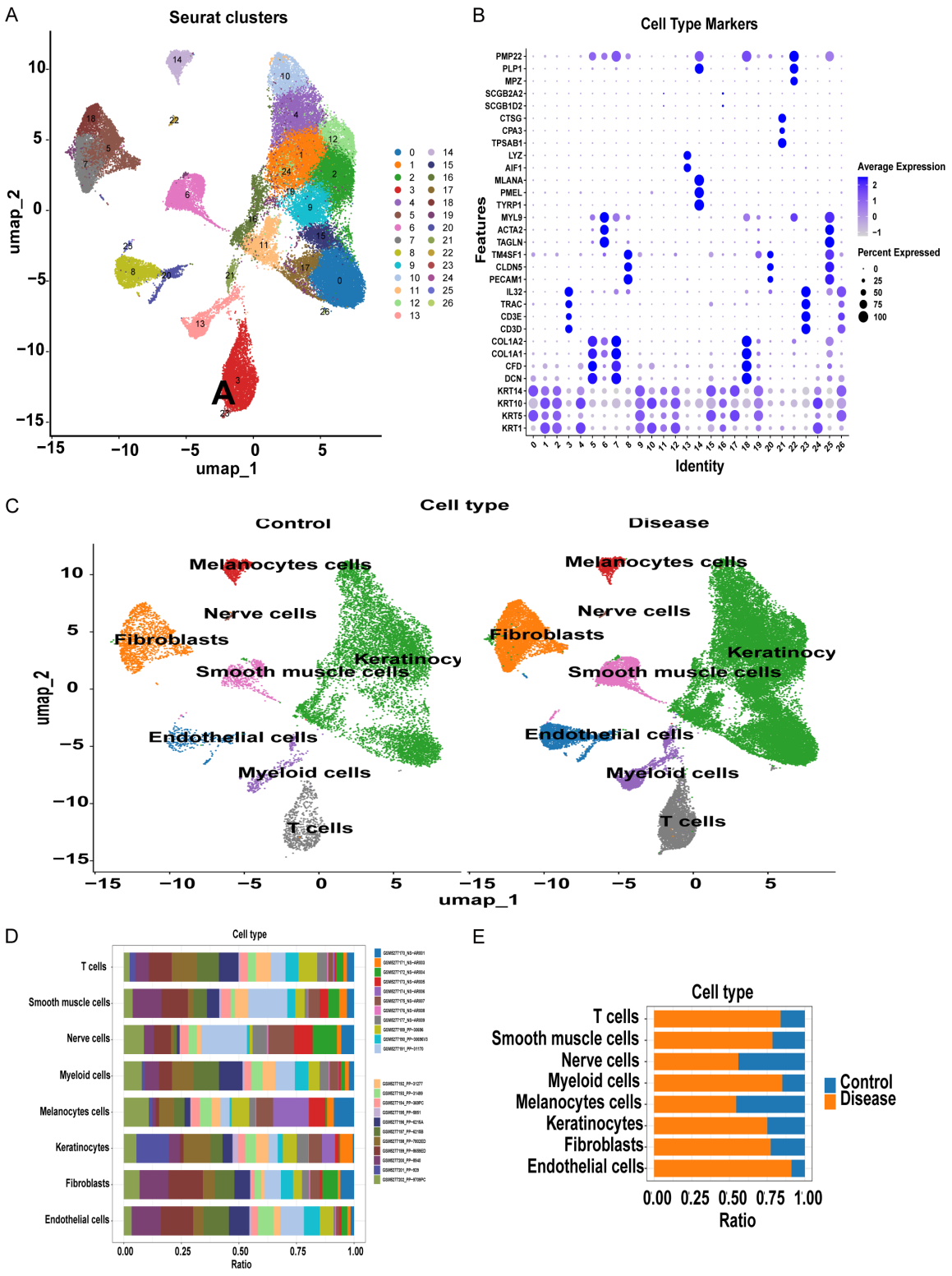


Figure 1. Single-cell transcriptomic landscape of psoriatic and normal skin. A. UMAP visualization of the 27 distinct cell clusters identified across all integrated samples. B. Dot plot showing the expression levels and percentages of classical marker genes used for cell type annotation across the 27 clusters. C. UMAP plots of the annotated major cell types split by the normal control group (left) and the psoriasis disease group (right). D. Stacked bar plot showing the proportional distribution of various cell types across individual samples. E. Bar plot comparing the overall relative proportions of different cell types between the Control and Disease groups, highlighting the expansion of T cells and myeloid cells in psoriasis.

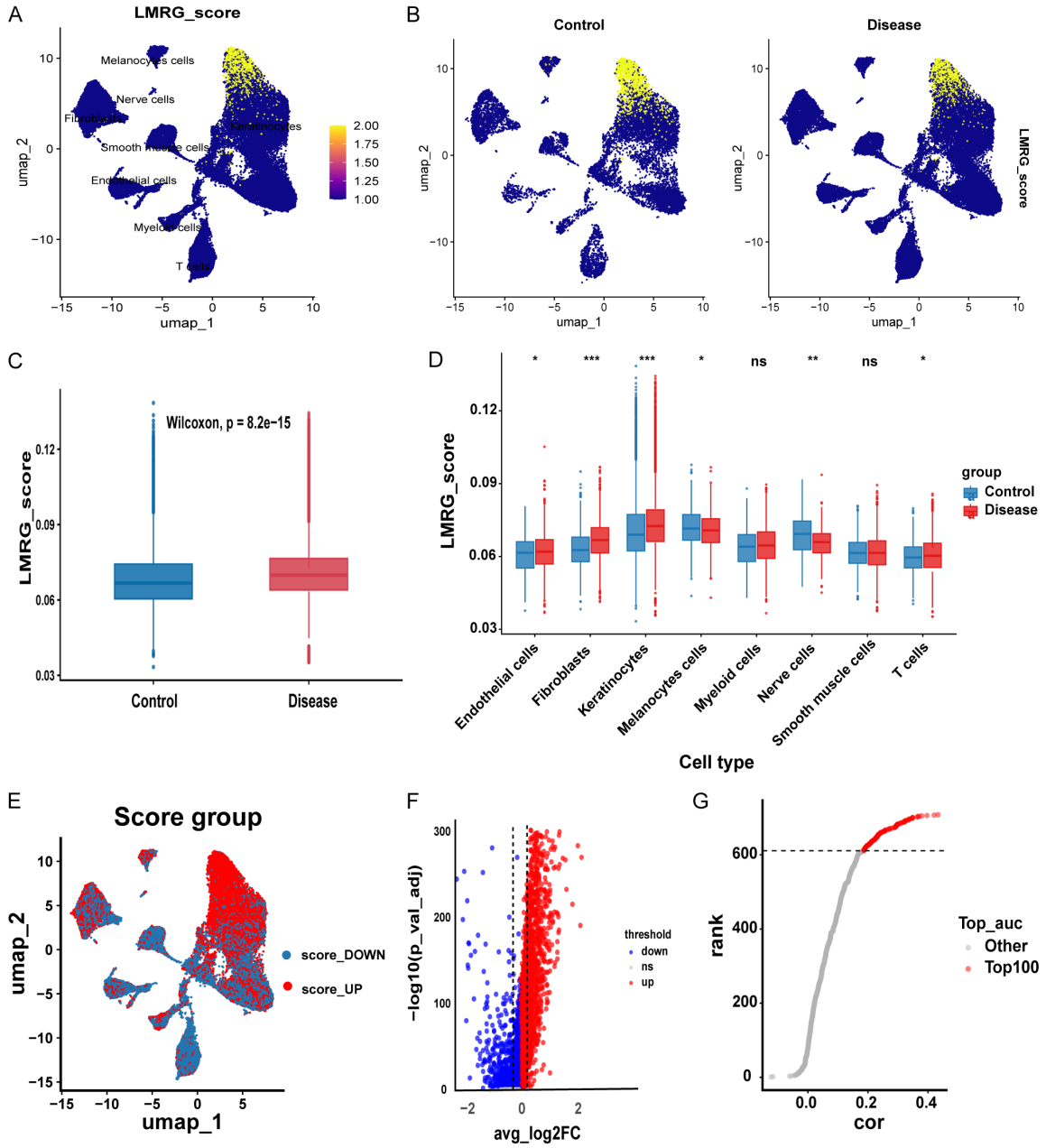


Figure 2. Single-cell lipid metabolism activity scoring reveals metabolic reprogramming in psoriatic keratinocytes. A. UMAP feature plot visualizing the overall lipid metabolism-related gene (LMRG) scores calculated via the AUCell algorithm. B. UMAP plots of LMRG scores separated by the Control and Disease groups. C. Boxplot showing the significant elevation of overall LMRG scores in the Disease group compared to the Control group (Wilcoxon test, p = 8.2e-15). D. Comparison of LMRG scores across distinct cell types between the Control and Disease groups, demonstrating that keratinocytes exhibit the highest metabolic activity. E. UMAP plot classifying cells into high (score_UP) and low (score_DOWN) metabolic states based on the median LMRG score. F. Volcano plot identifying the differentially expressed genes between the high and low metabolic state groups. G. Spearman correlation ranking of the top hub genes driving the hypermetabolic signature. Notes: Statistical significance in (C) and (D) was determined using the two-tailed Wilcoxon rank-sum test. ***P < 0.001.

genes screened by the three algorithms, 4 core machine learning genes (MLGs) were finally obtained: SQLE, SPTLC2, PLA2G4D, and PLBD1 (**Figure 3F**).

Expression analysis further confirmed that, compared to normal controls, all 4 genes were significantly upregulated in psoriatic lesions (**Figure 4A**). ROC curve analysis showed that

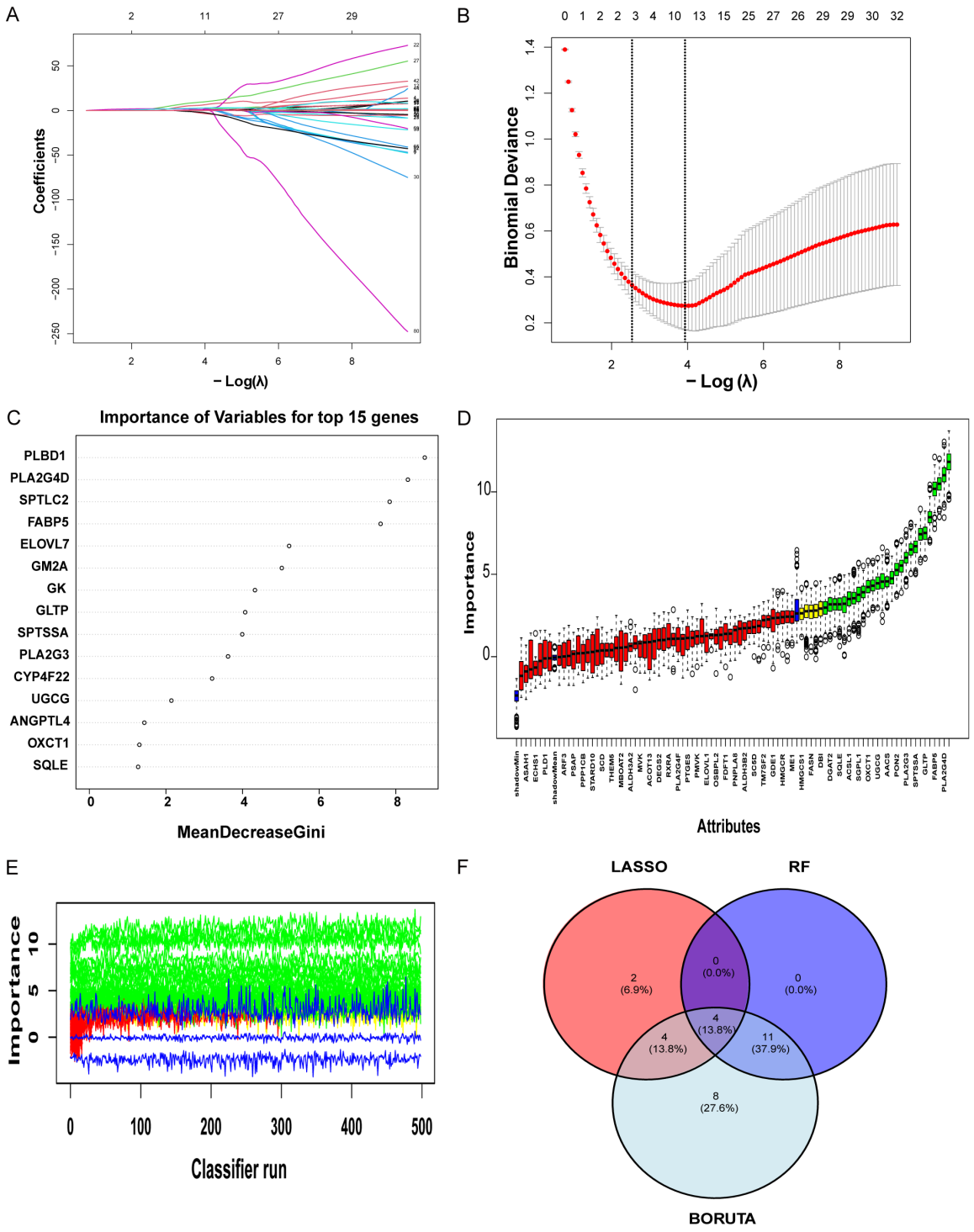


Figure 3. Identification of core diagnostic lipid metabolism genes via machine learning algorithms. A, B. Feature selection using LASSO regression analysis, showing the coefficient profile plot against the log(λ) sequence (A) and the partial likelihood deviance (B). C, D. Random Forest analysis ranking the top 15 critical genes based on the MeanDecreaseGini index (C) and variable importance distribution (D). E. Robust feature selection performed via the Boruta algorithm across 500 classifier runs. F. Venn diagram illustrating the overlap of core diagnostic genes identified by LASSO, Random Forest (RF), and Boruta algorithms, yielding 4 core hub genes (SQLE, SPTLC2, PLA2G4D, and PLBD1).

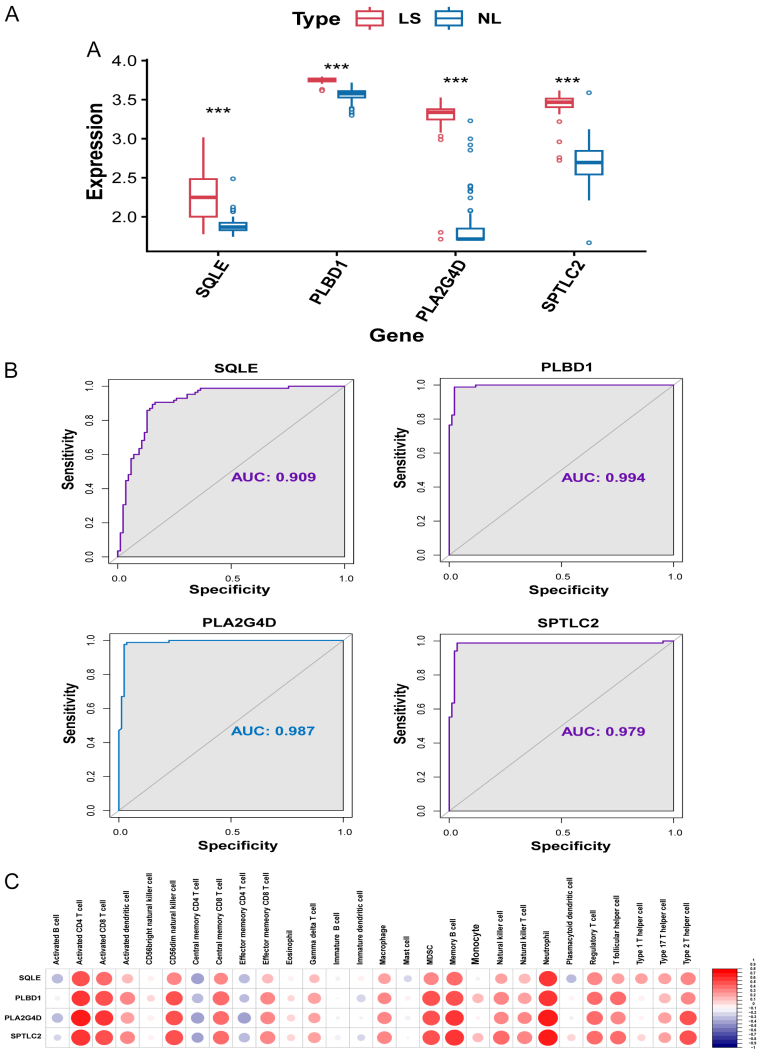


Figure 4. Validation of the core lipid metabolism genes and their correlation with immune infiltration. A. Boxplots comparing the expression levels of the four core genes (SQLE, PLBD1, PLA2G4D, SPTLC2) between lesional (LS) and non-lesional/normal (NL) tissues. $P < 0.001$. B. Receiver Operating Characteristic (ROC) curves and Area Under the Curve (AUC) values for the four core genes, demonstrating their high diagnostic efficacy for psoriasis. C. Bubble matrix plot revealing the ssGSEA-based correlation between the expression of the four core genes and the infiltration levels of various immune cell subsets (notably positive correlations with Th17 cells). Notes: Data in (A) are presented as mean ± SD. Statistical significance was determined using unpaired two-tailed Student's t-test. ***P < 0.001.

these 4 genes exhibited high diagnostic potential in the public dataset, with SQLE having an area under the curve (AUC) of 0.909, PLBD1 0.994, PLA2G4D 0.987, and SPTLC2 0.979 (**Figure 4B**). Furthermore, ssGSEA immune infiltration correlation analysis indicated that these 4 hub genes were broadly positively correlated with Th17 cell infiltration (**Figure 4C**), suggesting a link between abnormal lipid metabolism and T cell activation.

Cell communication analysis reveals an interaction between SQLE⁺ Keratinocytes and Th17 cells

We mapped the expression of the 4 core MLGs back to the scRNA-seq UMAP space. SQLE, PLBD1, PLA2G4D, and SPTLC2 were all expressed in the keratinocyte cluster, with SQLE having the highest expression in keratinocytes (**Figure 5A**). To elucidate the exact T cell subpopulations interacting with these metabolically altered keratinocytes, we extracted the T cell population and performed high-resolution sub-clustering. A total of 10 subclusters were obtained, annotated into 7 distinct functional states: CD4⁺ T cells, CD8⁺ T cells, Tregs, Th1 cells, NKT cells, Th17 cells, and proliferating T cells (**Figure 5B**). We stratified keratinocytes based on SQLE expression levels and constructed an intercellular communication network. Evaluating the interactions from SQLE⁺ keratinocytes to all other cell types revealed communication links with Th17 cells (**Figure 5C**). Signaling pathway analysis identified several key ligand-receptor pairs mediating this directional signal transmission, including CD99-CD99 (a broad adhesion molecule) and HLA-B-CD8A (more consistent with CD8⁺ T cell engagement rather than Th17-specific biology) (**Figure 5D**). We acknowledge that HLA-B-CD8A is more consistent with CD8⁺ T cell engagement rather than Th17-specific biology, and CD99-CD99 represents a general adhesion interaction. The specific molecular mediators responsible for SQLE-dependent Th17 recruitment remained to be identified and would require validation through ligand-receptor blocking experiments and chemokine/cytokine profiling. These bioinformatics pieces of evidence preliminarily suggest that the upregu-

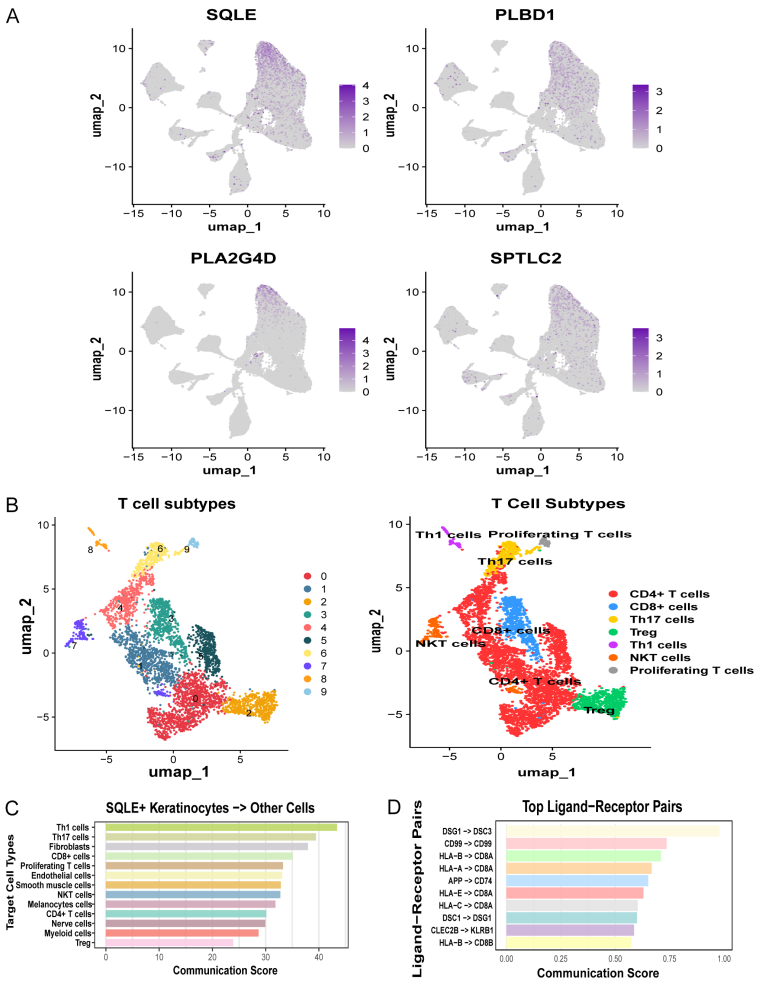


Figure 5. Cell-cell communication analysis reveals the interaction network between SQLE$^+$ keratinocytes and T cell subpopulations. A. UMAP feature plots showing the specific expression distribution of the four core machine learning genes (SQLE, PLBD1, PLA2G4D, and SPTLC2) across the entire single-cell landscape, predominantly localizing to keratinocytes. B. High-resolution re-clustering of the T cell population, displaying unsupervised subclusters (left) and annotated functional T cell subtypes including Th17 cells (right). C. Bar plot ranking the overall communication scores from SQLE$^+$ keratinocytes to various target cell types, highlighting prominent signaling interactions with Th1 and Th17 cells. D. Identification of the top-ranked ligand-receptor pairs mediating the directional signaling from SQLE$^+$ keratinocytes to the target immune cells.

lation of SQLE may be associated with altered secretory profile and surface ligand presentation of keratinocytes, potentially establishing an inflammatory microenvironment that communicates with and maintains Th17 cell function.

A high-fat diet (HFD) exacerbates IMQ-induced psoriasis-like lesions and amplifies the inflammatory cascade

Based on the aforementioned bioinformatics analysis, we found that SQLE, as a core diagnostic marker for psoriasis, holds a certain correlation with abnormal lipid metabolism and immune infiltration of Th17/neutrophils. SQLE encodes squalene epoxidase, which is the second rate-limiting enzyme in cholesterol synthesis. It has been confirmed in other diseases that it is also involved in lipid metabolism and immune regulation. Given that psoriasis patients in clinical settings frequently present with comorbidities like obesity and metabolic syndrome, we hypothesized that systemic lipid metabolism disorder may be a key trigger driving SQLE expression and aggravating local skin lesions. However, we acknowledge that HFD induces multiple systemic changes beyond hyperlipidemia, and the specific contribution of SQLE-mediated lipid metabolism requires further investigation.

To this end, we constructed an HFD combined with an IMQ-induced obese psoriasis mouse model. Compared to the ND+IMQ group, mice in the HFD+IMQ group exhibited significant weight gain (**Figure 6A**) and showed a marked upward trend in PASI scores regarding cutaneous macrophenotypic characteristics (**Figure 6B**). Liver H&E staining confirmed typical fatty liver-like changes in the HFD group (**Figure 6C**). The symptoms of erythema, scaling, and thickening of the skin lesions in the HFD+IMQ group appeared earlier and were more severe, presenting a significantly elevated trend in PASI scores (**Figure 6D**). Serological tests showed that the serum levels of total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C) in the HFD group were significantly increased (**Figure 6E**).

Histopathological (H&E staining) analysis revealed increased epidermal acanthosis and

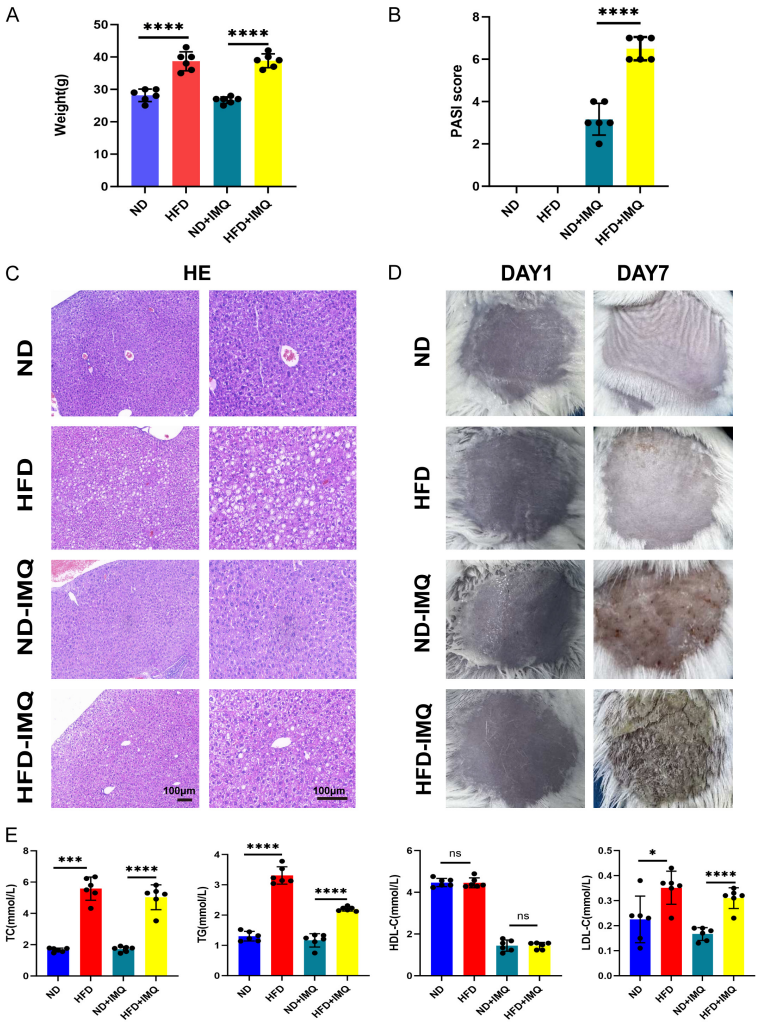


Figure 6. High-fat diet (HFD) exacerbates imiquimod (IMQ)-induced psoriasis-like skin lesions and induces systemic lipid metabolic disorders in mice. A. Body weight of mice. B. Psoriasis Area and Severity Index (PASI) scores reflecting the severity of cutaneous macrophenotypic characteristics (erythema, scaling, and thickening) in each group. C. Representative H&E staining of liver tissues (scale bar = 100 μm) showing typical fatty liver-like changes in HFD-fed mice. D. Representative macroscopic photographs of dorsal skin lesions on Day 1 and Day 7, demonstrating earlier onset and more severe symptoms in the HFD+IMQ group. E. The levels of total cholesterol (TC), triglycerides (TG) and low-density lipoprotein cholesterol (LDL-C), as well as high-density lipoprotein cholesterol (HDL-C) in each group. Notes: Data are presented as mean ± SD (n = 6 per group). Statistical significance was determined using unpaired two-tailed Student's t-test. ns, not significant, *$P < 0.05$, ***$P < 0.001$, ****$P < 0.0001$.

denser inflammatory cell infiltration in the dermis in the HFD+IMQ group, with the average epidermal thickness being much higher than that of the ND+IMQ group (**Figure 7A**). This is consistent with the abnormal lipid metabolism characteristics we observed in the bioinformatics analysis. In terms of immune infiltration, H&E staining confirmed an increased number of infiltrating neutrophils in the lesions of the HFD+IMQ group (**Figure 7B**), reproducing the bioinformatics prediction of "significantly enhanced neutrophil infiltration" at the in vivo animal level.

Lipid overload amplifies the local Th17 immune response by upregulating SQLE expression in keratinocytes

To clarify whether systemic lipid metabolism disorder is associated with local SQLE expression and the immune microenvironment in skin lesions, we performed histological and molecular biological correlative analyses. Immunohistochemistry (IHC) localization and quantitative analysis showed that under IMQ induction, SQLE was mainly localized in epidermal keratinocytes; notably, under the background of HFD-mediated lipid overload, the SQLE protein expression level in keratinocytes of the HFD+IMQ group was significantly higher than that in the ND+IMQ group (**Figure 8A**). Semi-quantitative analysis further confirmed that the SQLE staining intensity was significantly higher in the HFD+IMQ group than in the ND+IMQ group (**Figure 8C**). However, we did not measure SQLE enzymatic activity or cholesterol metabolic flux; therefore, we cannot conclude that elevated SQLE protein expression corresponds to increased enzymatic function or enhanced cholesterol synthesis. Given the positive correlation between SQLE and Th17 cell infiltration observed in our bioinformatics analysis, we further evaluated the in vivo effects of this metabolic change on local immune responses. Dual immunofluorescence staining revealed that, along with high SQLE expression, the number of infiltrating $CD4^+IL\text{-}17A^+$Th17 cells in

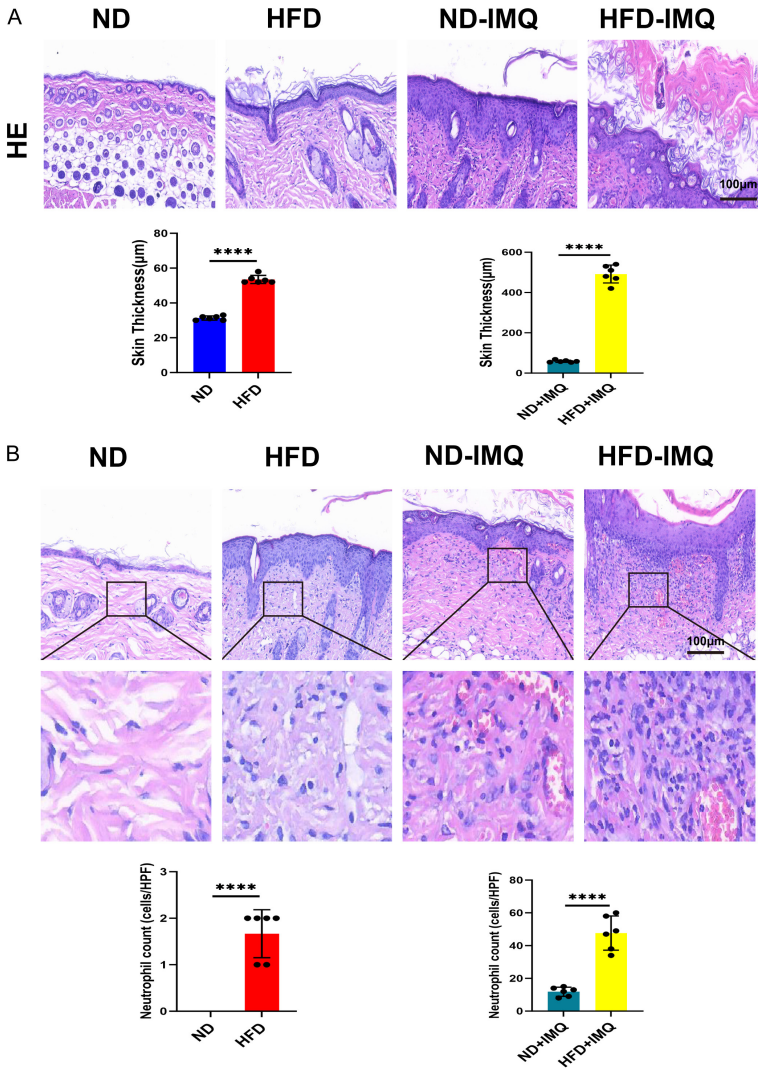


Figure 7. HFD aggravates histopathological changes and neutrophil infiltration in psoriatic skin lesions. A. Representative H&E staining of skin lesions (scale bar = 100 μm) and quantitative analysis of epidermal thickness. B. Representative H&E staining of skin lesions (scale bar = 100 μm) showing markedly increased neutrophil infiltration in the HFD+IMQ group, magnified views (400×) of the boxed dermal regions. Notes: Data are presented as mean ± SD (n = 6 per group). Statistical significance was determined using unpaired two-tailed Student's t-test. ****$P < 0.0001$.

the dermis of HFD+IMQ mice was higher than that in the conventional ND+IMQ group (**Figure 8B**). Quantitative analysis of multiple random fields also demonstrated a significantly increased infiltration density of Th17 cells in the HFD+IMQ group (**Figure 8D**). Moreover, ELISA of skin lesion homogenates showed that the secretion levels of the core pro-inflammatory effector molecules IL-17A and TNF-α were also significantly elevated in the local microenvironment of the HFD+IMQ group (**Figure 8E**). These in vivo observations are consistent with the trends predicted by our bioinformatics analysis, providing correlational evidence preliminarily suggesting an association between systemic lipid metabolism disorder and both SQLE overexpression and an enhanced Th17 response. However, causal inference awaits SQLE-specific genetic or pharmacological intervention studies.

Discussion

Through the multi-dimensional integration of single-cell transcriptomics, bulk sequencing, and machine learning algorithms, this study systematically constructed a single-cell atlas of lipid metabolism in psoriatic lesions and identifies SQLE as a potential candidate regulatory node associated with the interaction between keratinocytes and Th17 cells. More importantly, we utilized an HFD combined with the IMQ-induced mouse model to provide preliminary correlational validation of the above predictions in vivo. The results indicate that obesity-related metabolic milieu was associated with upregulated SQLE expression in epidermal keratinocytes, suggesting potential remodeling of local ligand presentation, which may be associated with the recruitment and amplification of the inflammatory response mediated by Th17 types and neutrophils in the dermis. We thereby propose that the "systemic lipid metabolism disorder may be associated with the Th17 cell immune cascade effect through upregulation of SQLE in keratinocytes" that may constitute a pathological regulatory axis, providing preliminary correlational evidence for understanding the molecular mechanism by which obesity exacerbates psoriasis. However, we emphasize that these findings are observational and hypothesis-generating; they do not establish causality.

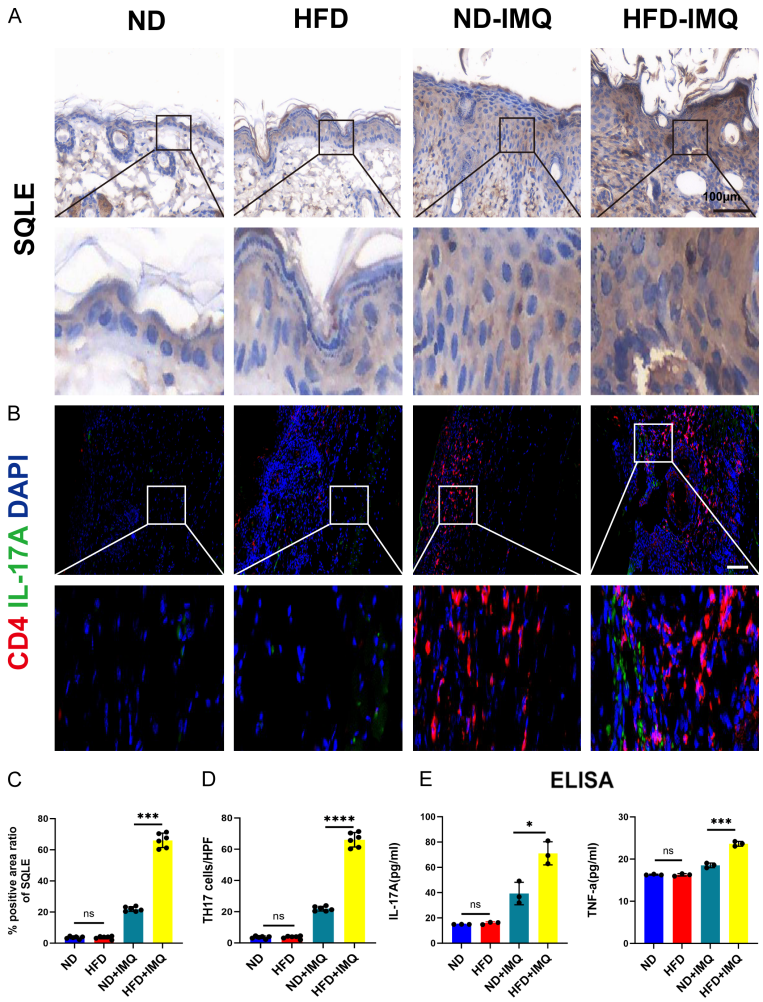


Figure 8. Obesity-associated metabolic milieu amplifies the local Th17 immune response by upregulating SQLE expression in epidermal keratinocytes. A. Representative immunohistochemical (IHC) staining of SQLE in skin lesions (scale bar = 100 μm), magnified views (400×) of the boxed epidermal regions. B. Representative multiplex immunofluorescence (mIF) staining of dermal $CD4^+IL\text{-}17A^+$Th17 cells (scale bar = 50 μm), magnified views (400×) of the boxed dermal regions. CD4 (red), IL-17A (green), DAPI (blue). C. Quantification of SQLE IHC staining intensity in skin lesions. D. Number of $CD4^+IL\text{-}17A^+$Th17 cells per high-power field in the dermis, derived from multiple random fields of dual immunofluorescence staining. E. ELISA quantification of IL-17A and TNF-α levels in skin lesion homogenates. Notes: Data are presented as mean ± SD (n = 6 per group). Comparisons were performed using unpaired two-tailed Student's t-test (HFD+IMQ vs. ND+IMQ). ns, not significant, $^*P < 0.05$, $^{***}P < 0.001$, $^{****}P < 0.0001$.

The association between abnormal lipid metabolism and psoriasis has been widely reported [13], but previous studies have mostly focused on serum lipid profile analysis or gene expression changes at the whole-tissue level, lacking cell-type-specific resolution at the single-cell level. This study preliminarily discovered via scRNA-seq analysis that lipid metabolism activity in psoriatic skin is highly concentrated in keratinocytes, which is consistent with the physiological role that epidermal barrier function requires large amounts of cholesterol and ceramides [14, 15]. While keratinocytes inherently possess active lipid metabolism for barrier function, the significant elevation of LMRG scores in psoriatic keratinocytes compared to normal controls suggests disease-associated metabolic reprogramming beyond physiological homeostasis. More importantly, the lipid metabolism score of psoriatic keratinocytes was significantly elevated compared to normal controls, strongly suggesting that keratinocytes undergo marked metabolic reprogramming under inflammatory conditions. As the second rate-limiting enzyme in the cholesterol synthesis pathway, SQLE has previously been studied mainly in the field of oncology. In hepatocellular carcinoma, pancreatic cancer, and head and neck squamous cell carcinoma, high SQLE expression can induce tumor-associated macrophage polarization and inhibit $CD8^+$ T cell function through metabolic reprogramming, thereby promoting immune evasion [8, 16, 17]. However, this study observed that the expression pattern of SQLE in psoriasis manifests differently from that in the oncology field: its expression is positively correlated with Th17 cell infiltration rather than immunosuppression. This tissue-specific difference may be attributed to the intrinsic difference in microenvironmental contexts - psoriasis represents a typical state of immune activation, whereas tumors feature an immunosuppressive microenvironment. In addition, while the other three lipid metabolism-related genes (PLBD1, PLA2G4D, SPTLC2) were also identified as core diagnostic markers, SQLE

was prioritized for functional investigation because it exhibited the most restricted and highest expression in keratinocytes and serves as a rate-limiting enzyme with a clear metabolic-immune link. Some studies have reported changes in SQLE expression in the liver and adipose tissue of obese mice. This study confirmed in the skin that HFD-induced hyperlipidemia can significantly increase the SQLE protein expression in epidermal keratinocytes, providing a molecular link for "lipid metabolism disorder - skin inflammation". The role of Th17 cells in psoriasis has been widely recognized: the IL-23/Th17 axis is the core of chronic inflammation in psoriasis, and IL-17A directly induces keratinocyte proliferation and the production of antimicrobial peptides and chemokines [18]. By re-clustering T cell subpopulations, this study confirmed the presence of the Th17 cell subset in psoriasis, and through CellChat analysis, outlined for the first time the cell communication relationship between $SQLE^+$ keratinocytes and Th17 cells. This finding provides a preliminary molecular explanation for obesity exacerbating psoriasis by upregulating SQLE. We acknowledge that the ligand-receptor pairs identified by CellChat, such as HLA-B-CD8A, are not specific to Th17 cells and may represent broader T cell-keratinocyte interactions. The specific molecular mediators responsible for SQLE-dependent Th17 recruitment remain to be identified and will require validation through ligand-receptor blocking experiments and chemokine/cytokine profiling.

The core value of this study lies in exploring the potential interaction mechanism between the lipid metabolism rate-limiting enzyme SQLE and the local immune microenvironment in psoriasis. Traditional research on the pathogenesis of psoriasis has long focused on the Th17-mediated immune cascade: starting from dendritic cell activation releasing IL-12/IL-23, which respectively drives Th1 cells (secreting IFN-γ) and Th17 cells (secreting IL-17) activation, forming a classical inflammatory model centered on adaptive immune dysregulation [19]. However, our data speculate that high SQLE expression in epidermal keratinocytes may act as a metabolic stress signal, participating in the remodeling of the local immune microenvironment. Through single-cell communication predictions and preliminary in vivo observations, keratinocytes with high SQLE expression exhibit an interactive phenotype specifically enhancing crosstalk with Th17 cells and neutrophils. Under the background of obesity-associated metabolic milieu caused by obesity, the lipid metabolism reprogramming occurring in epidermal structural cells (keratinocytes) may release specific chemokines and pro-inflammatory mediators, providing a "permissive" inflammatory microenvironment for the abnormal recruitment of Th17 cells in the dermis and the release of pro-inflammatory factors such as IL-17A and TNF-α, thus linking metabolic changes with immune activation. This finding suggests that lipid metabolism disorder is not merely a complication but may participate in and substantially amplify the local immune-inflammatory response in psoriasis through SQLE, a potential node.

At the clinical translational level, the findings of this study do not stop at the theoretical stage but provide a new perspective for the clinical management of refractory psoriasis patients complicated with metabolic syndrome: First, this study may contribute to risk stratification and efficacy prediction for patients. In clinical practice, psoriasis patients with comorbid obesity often exhibit higher primary or secondary treatment resistance to biologics [20, 21]. As a potential connection point between epidermal lipid metabolism and Th17 immune activation, SQLE expression levels may serve as a novel biomarker for predicting the efficacy of targeted immunotherapy in obese patients. Second, this study provides an exploratory strategy for "metabolic-immune dual-targeting" combined therapy. Terbinafine, a clinically available SQLE inhibitor, has an excellent safety profile [22]. The mechanisms we observed suggest that for refractory cases with poor responses to traditional biologics or accompanied by dyslipidemia, attempting to combine standard anti-inflammatory therapies with terbinafine or statins (upstream in its pathway) may indirectly block the "keratinocyte-Th17cell" pro-inflammatory communication loop by inhibiting local SQLE expression. This "drug repurposing" adjuvant therapy strategy may provide a novel clinical option that is both cost-effective and safe for overcoming clinical biologic resistance. Indeed, existing epidemiological studies support that statins can exert anti-inflammatory effects and improve psoriasis by downregulating cholesterol metabolism [23], which further corroborates our research rationale.

This study also has certain limitations. First, regarding verification of causal relationships, although the animal model confirmed that HFD could upregulate SQLE expression and aggravate skin lesions, gain- and loss-of-function experiments involving keratinocyte-specific SQLE knockout or overexpression were not conducted. Therefore, the exact causal relationship between SQLE upregulation and Th17 infiltration still needs further confirmation through genetic interventions. We propose that future studies using keratinocyte-specific SQLE conditional knockout mice and topical terbinafine treatment in the HFD+IMQ model would directly test whether SQLE is necessary and sufficient for Th17 recruitment and psoriatic inflammation. Second, in clinical validation, all bioinformatics analyses in this study were based on public databases, and animal experiments were based on mouse models. We have not yet directly validated the correlation between SQLE expression and Th17 infiltration in clinical samples from human psoriasis patients (especially in obese and non-obese subgroups), nor have we evaluated the association between SQLE expression and BMI, PASI scores, or treatment responses in patients. Third, our HFD model induces a complex array of systemic alterations including obesity, adipose tissue inflammation, hepatic steatosis, hormonal changes, insulin resistance, and gut microbiota dysbiosis. Without paired feeding, isocaloric controls, or specific lipid supplementation, we cannot attribute the exacerbated psoriasiform dermatitis specifically to hyperlipidemia versus other HFD-induced metabolic effects. Future studies employing lipid emulsion infusion, cholesterol-supplemented diets, or weight-matched pair-feeding designs are needed to dissect the specific contribution of circulating lipids. Fourth, we did not perform in vitro functional experiments on keratinocytes. SQLE overexpression or knockdown in HaCaT cells or primary keratinocytes, followed by assessment of cholesterol metabolism, IL-17-related inflammatory responses, and chemokine production, would be essential to establish the cellular mechanisms by which SQLE modulates keratinocyte-Th17 crosstalk. Such experiments would allow us to determine whether SQLE-mediated metabolic changes directly influence the secretion of chemokines (e.g., CCL20, CXCL8) and pro-inflammatory mediators involved in recruiting and activating Th17 cells. Fifth, an important limitation is the absence of SQLE enzymatic activity assays. While we observed elevated SQLE protein expression in keratinocytes under HFD conditions, we did not measure the conversion of squalene to 2,3-oxidosqualene or downstream cholesterol/oxysterol production. Future metabolomic studies measuring cholesterol synthesis intermediates and oxysterol species are needed to determine whether SQLE protein upregulation translates into increased metabolic flux. Finally, how SQLE upregulation specifically alters the functional state of keratinocytes-whether it influences the composition of cell membrane lipid rafts through cholesterol/oxysterol products and consequently affects the localization and signal transduction of membrane receptors (such as TLR, IFNGR)-these downstream molecular mechanisms remain unelucidated in this study and urgently require in-depth exploration through in vitro cellular experiments.

We propose that future studies should include in vitro experiments with SQLE overexpression or siRNA-mediated knockdown in HaCaT cells or primary human keratinocytes to assess cholesterol metabolism via LC-MS/MS, cytokine/chemokine production via ELISA and qPCR, and their effects on Th17 cell chemotaxis and activation in co-culture systems. In vivo experiments using keratinocyte-specific SQLE conditional knockout mice and topical terbinafine treatment are needed to determine whether SQLE is necessary and sufficient for Th17 recruitment and psoriatic inflammation; and clinical validation in human psoriasis patients, stratifying by BMI and treatment response, are required to assess the correlation between SQLE expression, Th17 infiltration, and clinical outcomes.

Conclusion

This study identified SQLE, through single-cell transcriptomics and machine learning, as a candidate lipid metabolism gene associated with psoriatic keratinocytes and suggested potential crosstalk with Th17 cells. In an obese psoriasis mouse model, obesity-associated metabolic milieu was associated with upregulated keratinocyte SQLE expression, exacerbated skin inflammation, and amplified Th17 responses. Our correlational findings suggest

SQLE may serve as a critical metabolic-immune hub potentially linking obesity to psoriasis aggravation and suggest that targeting SQLE may offer a novel therapeutic strategy for psoriatic patients with metabolic syndrome. Future studies using conditional knockout mice and clinical samples are warranted to validate causality and translational potential. We also emphasize that the specific molecular mediators of SQLE-dependent Th17 communication and the isolated contribution of hyperlipidemia versus other HFD effects require further investigation.

Disclosure of conflict of interest

None.

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