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ORIGINAL RESEARCH

Unsaturated Fatty Acid Metabolic Reprogramming in Psoriatic Skin Drives Inflammation and Predicts Response to Biologic Therapy

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Purpose: Psoriasis is frequently associated with dyslipidemia, yet the role of specific unsaturated fatty acid (UFA) metabolic pathways in disease pathogenesis and treatment response remains poorly understood. This study aimed to characterize the landscape of UFA metabolic reprogramming in psoriasis and evaluate its clinical relevance for predicting response to biologic therapy.

Patients and Methods: We performed an integrated multi-omics analysis incorporating transcriptomic data from human psoriatic lesions, single-cell RNA sequencing, and lipidomic profiling. Gene set variation analysis (GSVA) was used to evaluate UFA pathway activity. Logistic regression and LASSO were employed for biomarker selection and predictive modeling.

Results: We identified eight significantly dysregulated UFA metabolic pathways in psoriatic lesions, six of which were associated with key pathogenic processes in psoriasis. All pathways were reversibly modulated by biologic agents targeting TNF-α, IL-12/23, and IL-17A. We derived a three-gene biomarker signature (PLA2G4D, PLA2G4A, and FADS2) that robustly predicts response to IL-12/23 inhibition prior to treatment initiation (AUC = 0.902). Single-cell RNA sequencing revealed keratinocytes as the primary cellular contributors to UFA metabolism and identified an expanded PLA2G4D-high keratinocyte subpopulation in psoriatic skin, which was associated with the accumulation of Lysophosphatidylcholine (LysoPC) and Lysophosphatidylethanolamine (LysoPE).

Conclusion: Our findings elucidate the pathway-level metabolic basis of psoriasis inflammation and provide a clinically applicable tool for predicting response to biologic therapy. The results highlight the importance of UFA metabolic reprogramming in psoriatic pathogenesis and offer new avenues for treatment personalization.

Keywords: unsaturated fatty acid metabolism, psoriasis, biologic therapy, predictive biomarkers, keratinocyte, PLA2G4D

Introduction

Psoriasis is a chronic, immune-mediated inflammatory skin disease that affects millions worldwide, imposing substantial burdens on physical and psychosocial health, and overall quality of life.[1] Although biologic agents targeting specific immune pathways—such as TNF-α, IL-17, and IL-12/23—have revolutionized psoriasis treatment, significant clinical challenges remain.[2–4] A considerable proportion of patients exhibit inadequate response or loss of efficacy over time, and some develop adverse effects including anti-drug antibodies and paradoxical disease exacerbation.[3,5,6] These limitations underscore the urgent need to better understand the molecular drivers of psoriasis and to identify biomarkers that can predict treatment outcomes, thereby guiding personalized therapeutic strategies.

Accumulating evidence suggests that metabolic dysfunction plays a key role in psoriasis pathogenesis and progression.[7] In particular, psoriasis shows a well-documented comorbidity with metabolic syndrome and dyslipidemia.[8,9] This connection is underpinned by shared pathophysiological mechanisms, including chronic systemic inflammation, altered adipokine profiles, and insulin resistance, which collectively perturb lipid homeostasis and amplify immune activation. While these associations

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are epidemiologically established, the specific contributions of lipid metabolic pathways—especially those involving unsaturated fatty acids (UFAs)—to disease mechanisms and treatment response remain largely elusive.[10] UFAs are not only structural components of cellular membranes but also precursors of bioactive lipid mediators that regulate inflammation, proliferation, and immune cell function. Despite their potential significance, a systematic profiling of UFA metabolism in psoriasis and its modulation by biologic therapies has not been comprehensively conducted.

In this study, we aimed to systematically characterize UFA metabolic reprogramming in psoriasis and evaluate its clinical and therapeutic relevance. Using an integrated multi-omics approach—combining transcriptomic, single-cell, and metabolomic data—we sought to: (1) identify dysregulated UFA metabolic pathways in psoriatic skin; (2) assess their dynamic response to biologic agents; (3) derive a pathway-based signature predictive of treatment outcome; and (4) pinpoint key cellular contributors and molecular mediators of UFA-driven inflammation. Our findings reveal a profound imbalance in UFA metabolism that correlates with both disease severity and treatment response, establish keratinocytes as central executors of inflammatory lipid remodeling, and propose a novel biomarker panel for predicting response to IL-12/23 inhibition. These insights not only deepen our understanding of psoriatic pathophysiology through a metabolic lens but also open new avenues for therapeutic stratification and personalized intervention.

Materials and Methods

Data Retrieval

RNA sequencing (RNA-seq) datasets were obtained from the Gene Expression Omnibus (GEO) database (Supplementary Table S1). The GSE14905 dataset included 33 psoriatic lesional samples and 21 normal skin samples.[11] The GSE117239 dataset comprised 324 samples from patients treated with either Ustekinumab or Etanercept across multiple time points, forming the primary analysis cohort for this study, which included 42 ustekinumab-treated and 29 etanercept-treated patients with transcriptomic data at baseline and week-12 response assessment.[12] The GSE137221 and GSE201827 datasets provided lesional skin samples collected at baseline and following Secukinumab treatment, from which 38 secukinumab-treated patients with baseline and week-12 data were included in the cohort.[13] Additionally, single-cell RNA-seq data were acquired from the GSE162183 dataset, which contains profiles from 3 normal skin and 3 psoriatic lesion samples.[14] Metabolomic data were sourced from a 2023 study by Qian Song et al, which included samples from 10 plaque psoriasis patients and 10 healthy controls.

Pathway-Score Calculation for UFA Metabolism

Eleven UFA metabolism pathways were curated from the Molecular Signatures Database (MSigDB) via GSEA (Supplementary Table S2).[15] Gene sets corresponding to these pathways were compiled (Supplementary Table S3), and pathway enrichment scores were calculated using the ssGSEA algorithm implemented in GSVA (v2.2.0) under R.[16]

LASSO and Logistic Regression Analyses

To reduce feature dimensionality and identify genes most predictive of treatment response, least absolute shrinkage and selection operator (LASSO) regression was applied using the glmnet package in R. The optimal penalty parameter (λ) was determined through cross-validation to maximize model simplicity while retaining predictive accuracy. Genes selected by LASSO were subsequently incorporated into a logistic regression model constructed with the rms package to establish a clinical outcome prediction model.

Single-Cell RNA-Seq Analysis

Single-cell data were processed and annotated using the Seurat package.[17] Cell types were identified based on canonical marker genes described in the original publication. Dimensionality reduction was performed using the first 20 principal components, selected according to an elbow plot. Clustering was carried out with a resolution parameter of 0.8 and a neighbor count between 5 and 25. Keratinocytes, immune cells, endothelial cells, and fibroblasts were subset for further investigation. The AddModuleScore function was used to evaluate the activity of key UFA metabolism pathways within each cell subpopulation.

Statistical Analysis

All statistical analyses were performed using R software (v4.2.1) and relevant R packages. Comparisons between two independent groups were conducted using the Wilcoxon rank-sum test. For comparisons involving multiple time points against baseline, the Dunnett test was applied. Within-subject comparisons before and after treatment were assessed using the paired Wilcoxon test. Correlation analyses were performed using Spearman's rank correlation test. A two-tailed p-value of less than 0.05 was considered statistically significant.

Results

Bidirectional Dysregulation of Unsaturated Fatty Acid Metabolism Characterizes Psoriatic Lesions

To elucidate dysregulation of UFA metabolism in psoriasis pathogenesis, we conducted a pathway-based bioinformatic analysis. Gene sets representing 11 key UFA metabolism pathways were curated from the GSEA database. RNA-seq data from psoriatic lesional skin and healthy control skin were obtained from the GSE14905 dataset. Gene Set Variation Analysis (GSVA) was employed to calculate pathway enrichment scores for all samples. Principal component analysis (PCA) based on GSVA scores revealed a distinct separation between psoriatic lesional and healthy skin samples within the first two principal components (Figure 1A). Significant inter-group differences were observed for PC1 ($p = 4.6 \times 10^{-9}$, Figure 1B) and PC2 ($p = 3.1 \times 10^{-5}$, Figure 1C), confirming systemic remodeling of UFA metabolism in psoriatic lesions. Comparative analysis identified 8 UFA metabolism pathways with significant alteration in psoriatic lesions ($p < 0.05$; Figure 1D). Unsupervised hierarchical clustering partitioned the 8 pathways into two functionally antagonistic clusters: an upregulated cluster comprising five pathways: Linoleic acid metabolism, α-Linolenic acid metabolism, Arachidonic acid metabolism, Octadecanoid formation from linoleic acid, and Leukotriene metabolic pathway, the pronounced activation of which may suggest heightened pathogenic processes in lesional skin; and a downregulated cluster comprising three pathways: Prostaglandin and leukotriene metabolism in senescence, Docosahexaenoic acid oxylipin metabolism, and Prostaglandin synthesis and regulation, the suppressed activity of which may indicate impaired homeostatic functions (Figure 1E). Collectively, these findings demonstrate a significant and coordinated rewiring of UFA metabolic pathways, characterized by concurrent activation and suppression of specific routes, in psoriatic skin lesions.

Aberrant Unsaturated Fatty Acid Metabolism Exacerbates Psoriasis via Crosstalk with Pathological Signaling Axes

Established pathogenic mechanisms in psoriasis involve dysregulated proliferation and immune signaling pathways (IL-17, IL-22, IL-23, IL-17A-IL-22, TNF-α). To identify UFA metabolism pathways functionally linked to these core pathologies, we extracted gene sets corresponding to these 6 pathways. GSVA analysis confirmed pronounced enrichment ($p < 0.0001$) of all 6 pathways in psoriatic lesions versus normal skin (Figure 2A), serving as a positive control for the reliability of our analytical pipeline. Correlation analysis between the 8 dysregulated UFA metabolism pathways (Figure 1D) and these psoriasis signature pathways revealed distinct interaction patterns. Upregulated UFA pathways (Leukotriene metabolic, Octadecanoid formation, α-Linolenic acid, Linoleic acid, and Arachidonic acid metabolism) exhibited moderate positive correlations with all pathological pathways ($r > 0$, $p < 0.05$). Among downregulated UFA pathways, only Prostaglandin synthesis and regulation showed weak negative correlations ($r < 0$, $p < 0.05$) (Figure 2B). This integrated analysis identified 6 UFA pathways (5 upregulated, 1 downregulated) with strongest disease association. To further validate these associations at cellular resolution, we performed correlation analysis specifically within psoriatic keratinocytes at the single-cell level. This revealed moderate correlations between key UFA pathways—including Arachidonic acid, Linoleic acid, α-Linolenic acid metabolism, and Octadecanoid formation—and inflammatory pathways such as IL-22 signaling and IL-22–IL-17A signaling (Supplementary Figure A). Importantly, these correlations were absent in healthy control keratinocytes (Supplementary Figure B), highlighting a disease-specific relationship that reinforces the close association between keratinocyte-intrinsic UFA metabolism and core inflammatory signaling in psoriasis. These results suggest a model in which UFA metabolic perturbation is associated with psoriasis pathogenesis, potentially through the coordinated upregulation of pro-inflammatory lipid mediators that correlate with proliferation and cytokine axes.

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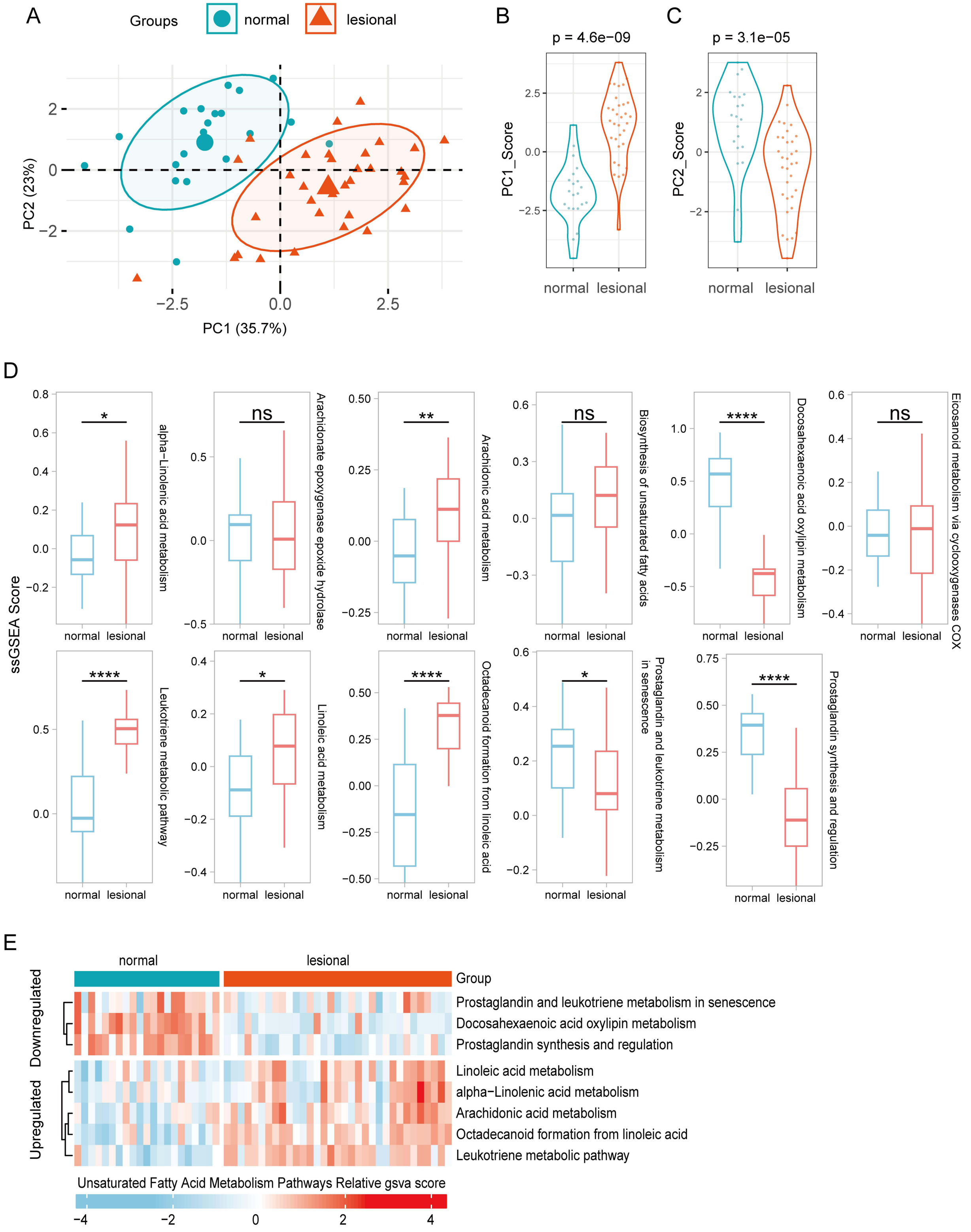

Figure 1 Dysregulation of Unsaturated Fatty Acid Metabolism in Psoriatic Skin. (**A**) Principal component analysis (PCA) of UFA metabolism pathway enrichment scores in normal skin and psoriatic lesion samples. Axes represent the first (PC1) and second (PC2) principal components. (**B** and **C**) Violin plots showing significant differences in PC1 (**B**) and PC2 (**C**) scores between normal and psoriatic samples. (**D**) Differential enrichment of 11 UFA metabolism pathways between psoriatic lesions and normal skin significance levels are denoted as *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001; ns, not significant. (**E**) Unsupervised clustering of the 8 significantly altered UFA pathways identified in (D), showing clear separation into 5 upregulated and 3 downregulated clusters in psoriasis. Data were obtained from GSE14905, including 21 normal samples and 33 psoriatic lesional samples.

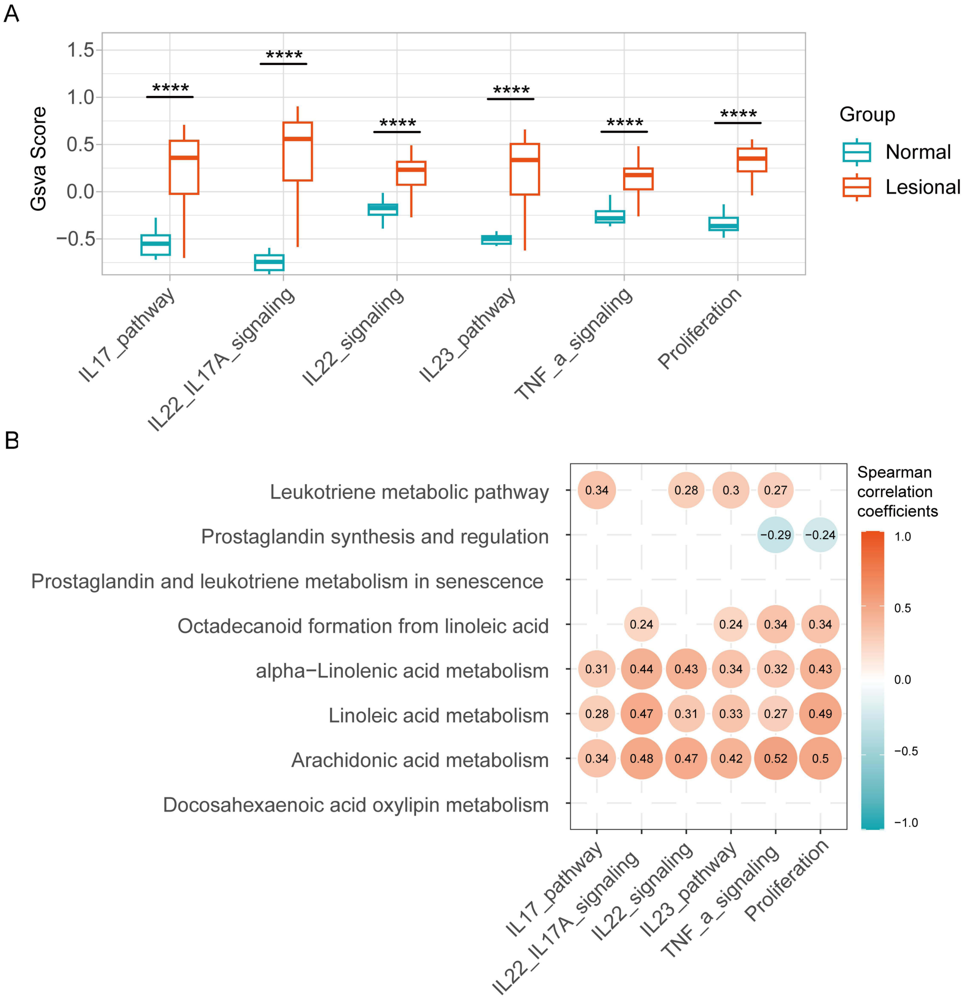

Figure 2 Aberrant Unsaturated Fatty Acid Metabolism Crosstalk with Psoriasis Pathological Signaling Axes. (**A**) The status of six psoriasis-specific pathways in lesional skin of patients compared to healthy controls significance levels are denoted as ****p < 0.0001. (**B**) Correlation analysis between eight dysregulated UFA metabolism pathway scores and six classical pathogenic signaling pathways. Red indicates a positive correlation, blue indicates a negative correlation, and blank denotes no statistical significance. The numbers within the circles represent Spearman correlation coefficients. The data of this Figure were obtained from GSE201827, including 17 normal samples and 70 psoriatic lesional samples.

Biologic Therapies Reverse Psoriasis-Associated Unsaturated Fatty Acid Metabolic Dysregulation

The clinical efficacy of biologic agents in psoriasis is well-established. To investigate whether modulation of aberrant UFA metabolism contributes to their therapeutic mechanism, we analyzed transcriptomic data from psoriatic lesions pre- and post-treatment with three biologics: the TNF-α inhibitor Etanercept, the IL-12/23 inhibitor Ustekinumab, and the IL-17A receptor blocker Secukinumab. We interrogated the 6 key UFA metabolism pathways previously identified as core dysregulated pathways in psoriasis pathogenesis. Following 12 weeks of treatment, all three agents induced significant reversal of the dysregulated UFA metabolic pathways (Figure 3A–C). Specifically, the five upregulated pathways (arachidonic acid, linoleic acid, α-linolenic acid, octadecanoid, and leukotriene metabolism) that were upregulated in lesions showed marked downregulation after treatment. Conversely, the prostaglandin synthesis pathway, which was suppressed in psoriasis, demonstrated significant recovery post-treatment.

To further characterize the temporal dynamics of this metabolic normalization, we analyzed longitudinal data from the GSE137221 dataset at baseline and on days 4, 12, 42, and 84 of Secukinumab treatment. Time-resolved ssGSEA analysis revealed progressive normalization of all 6 UFA pathways throughout treatment (Figure 3D), with early changes detectable as soon as day 42 and maximal effects achieved by week 12. Collectively, these findings demonstrate that

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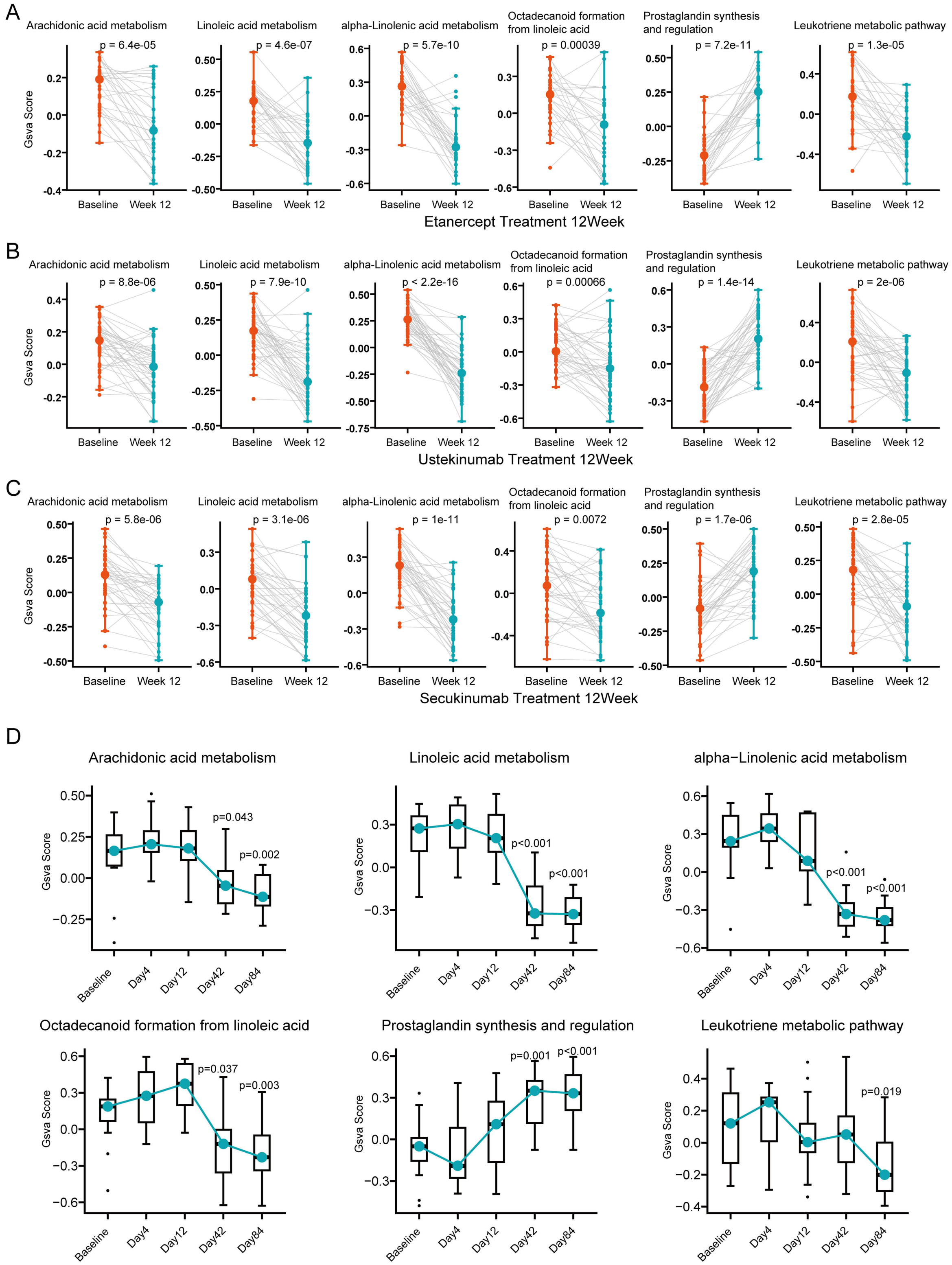

Figure 3 Biologic Therapies Reverse Psoriasis-Associated UFA Metabolic Dysregulation. (**A**–**C**) Changes in the six key UFA metabolic pathways (identified in Figure 2) in psoriatic lesions after 12 weeks of treatment with (**A**) etanercept (n=29; GSE117239), (**B**) ustekinumab (n=42; GSE117239), and (**C**) secukinumab (n=38; GSE201827). Pathways showing consistent reversal are highlighted. (**D**) Temporal dynamics of the six UFA pathways during secukinumab treatment at baseline, day 4, day 12, day 42, and day 84 (GSE137221; n=14 patients). Statistical significance versus baseline was assessed using Dunnett's test, with exact p-values indicated directly in the figure.

diverse biologic agents—spanning TNF-α, IL-12/23, and IL-17A inhibition—consistently reverse the dichotomous UFA metabolic dysregulation characteristic of psoriatic lesions. The 6 UFA pathways (Arachidonic acid metabolism, Linoleic acid metabolism, α-Linolenic acid metabolism, Octadecanoid formation, Prostaglandin synthesis and regulation, and Leukotriene metabolism) thus represent shared metabolic targets across distinct therapeutic modalities. Their coordinated normalization correlates with clinical improvement and may serve as both a potential biomarker of treatment response and a fundamental mechanism underlying therapeutic efficacy in psoriasis.

Baseline Unsaturated Fatty Acid Metabolism Determines Therapeutic Response to IL-12/23 Inhibition in Psoriasis

Having established that biologic therapy normalizes UFA metabolic imbalance, we next asked whether the pre-treatment metabolic state could predict the magnitude of therapeutic response. This question is clinically critical, given the substantial inter-patient heterogeneity in treatment efficacy and the current absence of reliable predictive biomarkers. We therefore hypothesized that the pre-treatment transcriptional activity of UFA metabolic pathways could predict outcomes to IL-12/23 inhibition. Patients were stratified into high- and low-response groups based on the median PASI improvement rate (86.86%) observed at 12 weeks post-treatment with Ustekinumab. We then analyzed the pre-treatment (baseline) expression levels of all 109 genes encompassed within the 6 UFA metabolic pathways that were previously shown to be consistently reversed by biologic treatment in these stratified cohorts. LASSO regression analysis identified a concise set of 12 prognosis-relevant genes (Figure 4A and B). Subsequent logistic regression confirmed 6 genes with statistically significant predictive value ($p < 0.05$; Figure 4C): Higher pre-treatment expression of three genes was associated with a greater likelihood of high response (OR > 1): PTGS2, PLA2G4D, and PLA2G4A. Higher pre-treatment expression of three genes was associated with a reduced likelihood of high response (OR < 1): PPARGC1A, FADS2, and CYP3A4.

We focused on developing a practical predictive model using a refined gene set. The individual predictive power of PLA2G4D (AUC = 0.755), PLA2G4A (AUC = 0.714), and FADS2 (AUC = 0.680) was significant (Figure 4D). A combined model integrating the baseline expression levels of these three genes demonstrated excellent predictive capability for forecasting 12-week treatment response (AUC = 0.902; Figure 4E). The model also exhibited outstanding calibration (Brier score = 0.128; Figure 4F), indicating a high degree of agreement between predicted and observed outcomes. In summary, we have derived and validated a novel three-gene biomarker signature (PLA2G4D, PLA2G4A, FADS2) from UFA metabolism pathways. This signature robustly predicts clinical response to Ustekinumab prior to treatment initiation, offering a potential tool for stratifying patients and personalizing therapeutic strategies.

Enrichment of a Pro-Inflammatory PLA2G4D-High Keratinocyte Subpopulation in Psoriasis Underlies the Prognostic UFA Metabolic Signature

To delineate the cellular basis of UFA metabolic dysregulation in psoriasis, we analyzed single-cell RNA-seq data (GSE162183) from four major cutaneous cell types (Figure 5B). Gene set enrichment analysis of the 6 previously identified dysregulated UFA pathways revealed distinct cell-type-specific activities: keratinocytes were the dominant contributors to α-linolenic acid, linoleic acid, and arachidonic acid metabolism, as well as octadecanoid formation; immune cells were primarily associated with leukotriene metabolism, prostaglandin synthesis, and also contributed to arachidonic acid metabolism and octadecanoid formation; fibroblasts showed involvement mainly in prostaglandin synthesis. Notably, α-linolenic acid and linoleic acid metabolism were uniquely and highly active in keratinocytes (Figure 5A). Feature plotting further confirmed pronounced upregulation of these pathways within a specific keratinocyte subpopulation in psoriatic lesions (Figure 5C and D).

Notably, this metabolically active keratinocyte subpopulation corresponded precisely to cells exhibiting high PLA2G4D expression, which was significantly expanded in psoriatic lesions compared to normal skin (Figure 5E and F). PLA2G4D catalyzes the hydrolysis of phospholipids to generate LysoPC, LysoPE, and free polyunsaturated fatty acids (PUFAs). Consistently, metabolomic profiling (LC-MS) revealed substantial accumulation of LysoPC and LysoPE in psoriatic lesions (Figure 5G). The released PUFAs are subsequently metabolized through coordinated enzymatic actions involving FADS2-mediated desaturation to form more unsaturated derivatives. This integrated network model

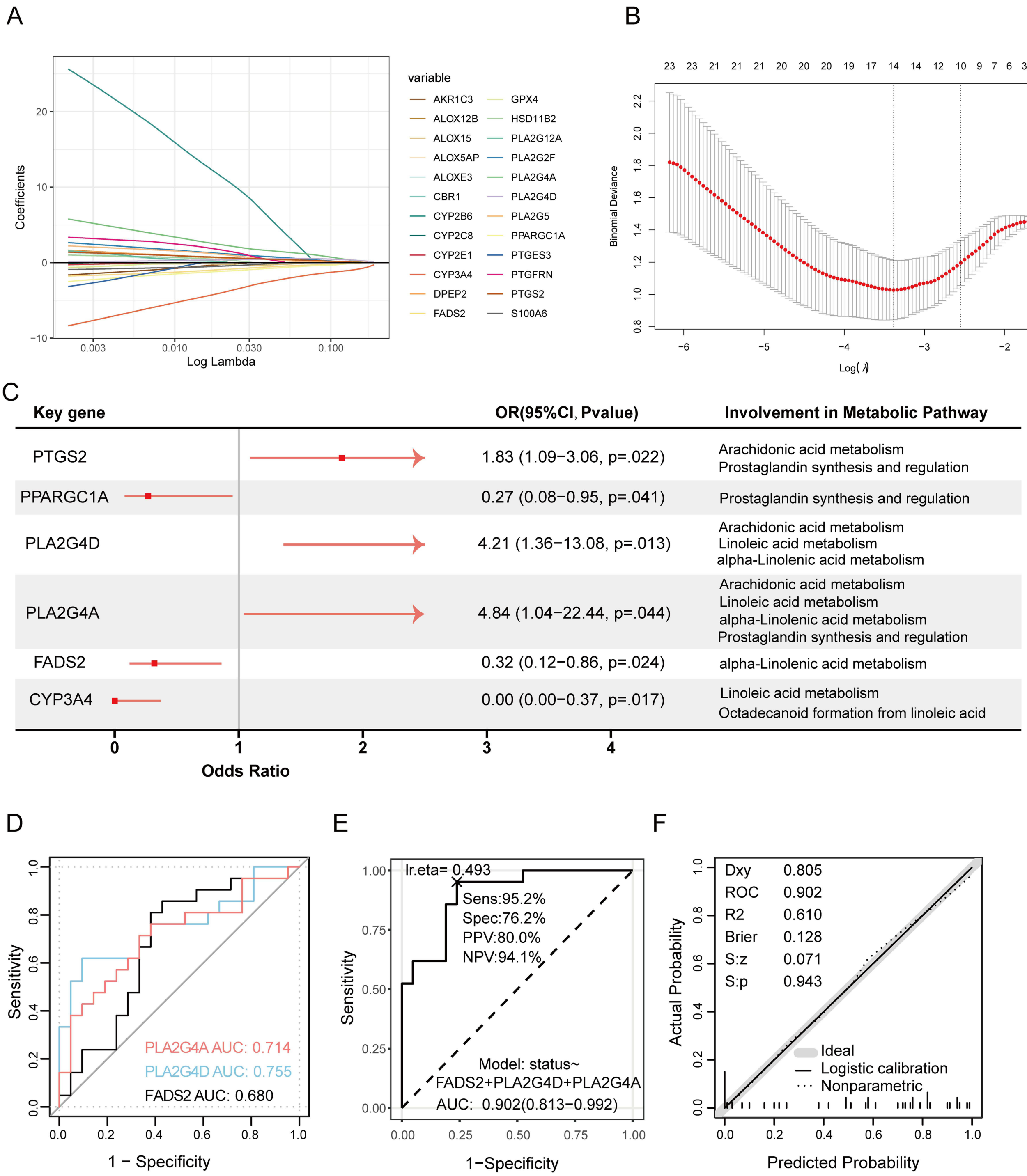

Figure 4 Baseline UFA Metabolism Predicts Response to IL-12/23 Inhibition in Psoriasis. (**A**) Coefficient profiles of 109 candidate genes in the LASSO regression. Each curve represents the coefficient path of a gene as the penalty parameter (λ) increases. (**B**) Selection of the optimal λ value via 10-fold cross-validation in LASSO regression. The vertical dashed line indicates the λ value that gives the most regularized model within one standard error of the minimum cross-validation error. (**C**) Forest plot displaying the six genes with significant predictive value for treatment response identified by logistic regression analysis. Odds ratios and 95% confidence intervals are shown. (**D**) Receiver operating characteristic (ROC) curves evaluating the individual predictive performance of PLA2G4D, PLA2G4A, and FADS2 gene expression at baseline. (**E**) ROC curve demonstrating the combined predictive power of the three-gene signature (PLA2G4D, PLA2G4A, and FADS2) for treatment response. (**F**) Calibration curve assessing the agreement between predicted probabilities and observed outcomes of the three-gene model. The dashed line represents perfect calibration. Data were derived from the GSE117239 dataset (n=42 patients treated with ustekinumab).

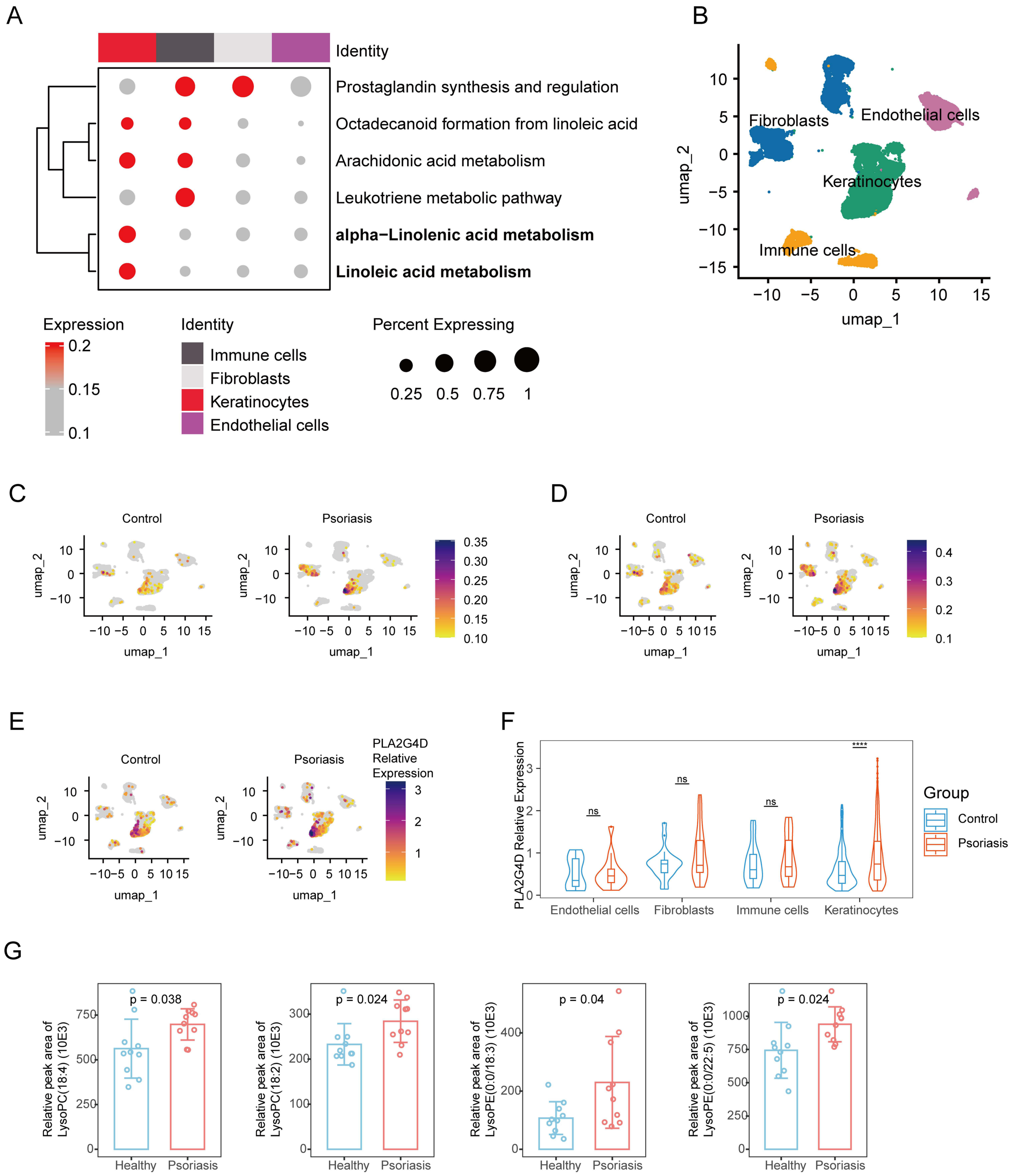

Figure 5 Single-Cell Analysis Identifies a pro-Inflammatory PLA2G4D-High Keratinocyte Subpopulation in Psoriasis. (**A**) UFA metabolism pathway scores across four major cutaneous cell types evaluated using the AddModuleScore function in Seurat. (**B**) UMAP visualization of single-cell RNA sequencing data showing the distribution of four major cell types in human skin. (**C**) FeaturePlot visualization showing keratinocyte-restricted enrichment of the linoleic acid metabolism pathway in psoriatic lesions. (**D**) FeaturePlot visualization showing keratinocyte-restricted enrichment of the α-linolenic acid metabolism pathway in psoriatic lesions. (**E**) FeaturePlot demonstrating specific PLA2G4D expression localized to a keratinocyte subpopulation. (**F**) Violin plots comparing PLA2G4D expression across cell subtypes between psoriatic and normal samples (Wilcoxon test, ****p < 0.0001). (**G**) Metabolomic validation by LC-MS showing significant accumulation of PLA2G4D-derived lipid metabolites (LysoPC and LysoPE) (n=10 per group, Wilcoxon test). All single-cell data were derived from the GSE162183 dataset (3 normal, 3 psoriatic samples). Metabolomic data were obtained from an independent validation cohort.

provides a framework to reconcile the divergent prognostic values of these biomarkers: the positive association between elevated PLA2G4D/PLA2G4A expression and favorable treatment response is consistent with a model in which biologics act by counteracting their associated pro-inflammatory lipid mediators. Conversely, elevated FADS2 expression correlates with poorer outcomes, which may involve the generation of inflammation-sustaining or therapy-impairing lipid species that are less susceptible to biological treatment.

Discussion

Our study provides a pathway-oriented perspective on psoriatic pathogenesis and treatment. Unlike conventional transcriptomic analyses that prioritize individual gene expression, our findings highlight that the integrated activity of metabolic pathways offers a more functionally coherent and clinically relevant understanding of the disease. By integrating transcriptomic, metabolomic, and single-cell data, we identified eight dysregulated UFA metabolic pathways, six of which—including linoleic acid, α-linolenic acid, and arachidonic acid metabolism—are centrally implicated in psoriatic inflammation. Notably, biologic therapies targeting TNF-α, IL-12/23, and IL-17A consistently reversed these metabolic alterations, underscoring the functional relevance of UFA pathways in treatment response. Furthermore, we derived a novel three-gene biomarker signature—PLA2G4D, PLA2G4A, and FADS2—from these pathways, which robustly predicts response to IL-12/23 inhibition prior to treatment initiation. Mechanistically, we observed a significant expansion and functional activation of a PLA2G4D-expressing keratinocyte subpopulation in psoriatic lesions drives the conversion of phospholipids into pro-inflammatory lipid mediators, including lysophospholipids and eicosanoids, thereby bridging cellular metabolism with inflammatory output.

Although the involvement of UFAs in chronic inflammatory skin diseases has long been hypothesized,[18] the precise routes through which lipid metabolism feeds the IL-23/IL-17/IL-22/TNF-α axis have remained fragmentary.[19] Our data now map six functionally distinct UFA pathways onto these established pathogenic circuits. The five up-regulated modules—leukotriene metabolism, octadecanoid formation, α-linolenic acid, linoleic acid and arachidonic-acid metabolism—converge on a surplus of bioactive lipids that act as co-agonists of the core cytokine network: 12/15-LO products derived from α-linolenic and linoleic acids amplify IL-6 and TNF-α transcription,[20] and AA-derived PGE_2 stimulates the IL-22 mRNA in T-cells,[21] thereby creating a self-amplifying lipid–cytokine loop that sustains epidermal hyperproliferation. Conversely, the single down-regulated module—prostaglandin synthesis and regulation—normally generates anti-inflammatory 15d-PGJ_2 that suppress STAT3 and NF-κB signalling;[22] its selective silencing removes a physiological brake on the same cytokine axes. Importantly, biologics that neutralize TNF-α or IL-23 not only dampen cytokine transcripts but also restore the prostaglandin module while down-regulating the five overactive pathways, indicating that the lipid signature is reversible and downstream of the primary cytokine drivers. Collectively, our findings position these six UFA pathways as proximal metabolic executors of the TNF-α/IL-23/IL-17 feed-forward circuit and as quantifiable surrogates for monitoring the depth of biological response in psoriasis.

A significant challenge in psoriasis management remains the unpredictability of treatment response and the lack of reliable predictive biomarkers.[23,24] Our study addresses this gap by demonstrating that pretreatment expression levels of six lipid-metabolizing genes stratify patients into two functionally distinct metabolic–immune endotypes. Elevated expression of PTGS2, PLA2G4D, and PLA2G4A—positively associated with treatment response—characterizes an endotype with enhanced arachidonic acid (AA)-mediated pro-inflammatory signaling,[25] wherein PLA2G4D/A release AA and PTGS2 converts it to prostanoids that amplify IL-23/Th17 signaling and immune infiltration, potentially increasing the inflammatory substrate targeted by biologics and thereby facilitating treatment response. Conversely, elevated expression of PPARGC1A, FADS2, and CYP3A4—negatively correlated with outcome—defines an endotype favoring anti-inflammatory eicosanoid production and drug clearance, attenuating the very inflammatory milieu upon which biologics act.[26,27] From these six candidates, we further refined a three-gene biomarker signature—PLA2G4A, PLA2G4D, and FADS2—that enables pre-therapeutic stratification for response to IL-12/23 inhibition. The predictive utility of this signature is mechanistically grounded in our single-cell findings, which identify a PLA2G4D-high keratinocyte subpopulation that serves as a metabolic hotspot coordinating a localized network wherein PLA2G4D releases free PUFAs and lysophospholipids and FADS2 mediates desaturation, providing a cellular basis for the prognostic value of the signature and bridging keratinocyte-intrinsic inflammation with treatment responsiveness. Notably, while our signature was derived from lesional skin biopsies, future clinical translation would benefit from exploring less invasive approaches. Measuring the corresponding lipid mediators, such as LysoPC and LysoPE, in serum or utilizing non-invasive skin sampling techniques could offer more feasible alternatives for biomarker assessment.

Beyond cell-autonomous effects, our single-cell data provide direct evidence for metabolic cross-talk between keratinocytes and immune cells in psoriatic lesions, further delineating cell-specific lipid metabolic programs that operate within the psoriatic microenvironment.[28] Our results demonstrate a striking compartmentalization of UFA metabolic pathways, with keratinocytes (particularly the identified PLA2G4D-high subpopulation) predominantly mediating the initial hydrolysis of α-linolenic acid and linoleic acid through PLA2G4D to release precursors such as arachidonic acid, whereas infiltrating myeloid cells (particularly monocyte-derived macrophages and dendritic cells) take over the synthesis of downstream inflammatory mediators, including leukotrienes and prostaglandins. This metabolic division of labor suggests a model of transcellular collaboration wherein keratinocyte-derived precursors are taken up and further metabolized by immune cells. Conversely, immune-derived cytokines (eg, IL-17, TNF-α) can further induce lipid-metabolizing enzymes in keratinocytes, potentially establishing a feed-forward inflammatory loop.[29] This cross-cell metabolic network, evidenced by our multi-omics data, may not only amplify inflammatory responses but also influence responses to biologic therapies targeting specific immune pathways. Our biomarker signature might capture the activity of this broader, collaborative inflammatory circuit, explaining its strong prognostic value for response to systemic immunomodulation.

Despite the insights gained, this study has several limitations that should be acknowledged. First, its conclusions are derived primarily from bioinformatic analyses of public datasets, which may be influenced by batch effects and unmeasured confounding factors such as prior treatment history or lesion heterogeneity. Second, the biomarker signature was identified from the GSE117239 cohort and lacks validation in independent external datasets, which currently are scarce due to the practical challenges of obtaining serial biopsies. Consequently, while the signature shows prognostic potential, its clinical applicability requires further validation and feasibility studies. Third, the signature was developed in cohorts treated primarily with ustekinumab; its generalizability to other biologic classes (eg, IL-23p19 inhibitors) remains unclear. Finally, although dietary UFA modulation shows promise in other inflammatory conditions, its direct impact on psoriasis treatment response remains empirically untested and represents a compelling direction for future investigation.

Conclusion

In summary, our work delineates the central role of UFA metabolic dysregulation in psoriasis. We identified a three-gene biomarker signature—PLA2G4D, PLA2G4A, and FADS2—that robustly predicts response to IL-12/23 inhibition, offering a clinically applicable tool for treatment personalization. Furthermore, we uncovered a pathogenic PLA2G4D-high keratinocyte subpopulation that drives inflammatory UFA metabolism and significantly contributes to psoriatic inflammation. Together, these findings refine the metabolic understanding of psoriasis and open new avenues for targeted interventions and personalized therapeutic strategies.

Abbreviations

UFA, Unsaturated Fatty Acid; AUC, area under the curve; PCA, Principal component analysis; GSVA, Gene set variation analysis; PUFAs, polyunsaturated fatty acids; AA, arachidonic acid; LysoPC, Lysophosphatidylcholine; LysoPE, Lysophosphatidylethanolamine; 15d-PGJ2,15-Deoxy-Delta-12,14-prostaglandin J2.

Data Sharing Statement

All data is from public databases and is open source. All data sources, tools, and codes were described in the Methods section.

Ethics Approval and Consent to Participate

This study utilized data from publicly available databases. All original studies from which these data were derived had obtained necessary ethical approvals from their respective institutional review boards and ensured full patient anonymity. The research protocol of this study was reviewed and approved by the Institutional Review Board (IRB)/Ethics Committee of The 940th Hospital of the Joint Logistic Support Force of the PLA. The need for individual patient consent was waived by the ethics committee as the study involved analysis of existing anonymized data.

Consent for Publication

All authors agreed to publish the manuscript.

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Disclosure

The authors report no conflicts of interest in this work.

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