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ORIGINAL RESEARCH

MAIT Cells with High PFN1 Expression Mediate Immune Activation and Metabolic Reprogramming in Psoriasis

Man-Ning Wu[1–3], Yue-Min Zou[1–3], Xiang-Nan Zhou[2,3], Sangwon Hong[1–3], Lei Wang[2,3], Yan-Ping Bai[2,3]

[1]Beijing University of Chinese Medicine, Beijing, 100029, People's Republic of China; [2]Department of Dermatology, China-Japan Friendship Hospital, National Center for Integrative Medicine, Beijing, People's Republic of China; [3]Department of Dermatology, China-Japan Friendship Hospital, Beijing, People's Republic of China

Correspondence: Yan-Ping Bai; Lei Wang, Email zhi@tsinghua.edu.cn; wanglei010zyy@163.com

Background: Psoriasis is a chronic inflammatory skin disease involving dysregulated immune responses and complex genetic factors. This study combines single-cell RNA sequencing (scRNA-seq), gene expression profiling, and genetic analysis to explore cellular and molecular contributors to psoriasis.

Methods: Single-cell RNA-seq data (n = 3 psoriasis, n = 2 control; GSE228421) were used for cell-type annotation and functional characterization. T cell subsets were analyzed for differentiation trajectories and cell-cell communication. Differentially expressed genes in mucosal-associated invariant T (MAIT) cells were evaluated by enrichment analysis. Candidate gene causality was tested via eQTL-based Mendelian randomization (MR) and supported by bulk RNA-seq validation.

Results: MAIT cells were enriched in psoriatic lesions and exhibited strong intercellular interactions. Functional analyses revealed activation of IL6-JAK-STAT3 signaling, TNF-NFκB pathway, and glycolysis in MAIT cells. MR identified RPS20 as a protective factor (OR = 0.5994, p = 0.011) and PFN1 as a potential risk gene (OR = 1.7229, p = 0.037), with PFN1 highly expressed in MAIT cells. Colocalization analysis showed no significant genetic overlap between PFN1 expression and psoriasis risk. Metabolic profiling revealed differential pathway involvement in PFN1+ and PFN1− MAIT cells.

Conclusion: Our integrative analysis highlights MAIT cells and PFN1 as likely contributors to psoriasis pathogenesis. These findings offer insights into immune and metabolic alterations, suggesting potential targets for therapeutic intervention.

Keywords: psoriasis, MAIT cells, PFN1, scRNA-seq, eQTL Mendelian randomization analysis

Introduction

Psoriasis is a multifactorial, chronic inflammatory skin disorder with a global prevalence of approximately 2%.[1] It is characterized by recurrent erythematous plaques, hyperproliferative keratinocytes, and aberrant immune cell infiltration. Triggers such as infections, trauma, and certain medications can initiate or exacerbate disease activity.[2] Among the immune components involved, both innate and adaptive immune cells play critical roles in disease onset and progression. Dendritic cells and macrophages stimulate T cells through cytokines like IL-23 and IL-12, promoting the differentiation of Th17 and Th1 cells, which subsequently produce IL-17, IL-22, and IFN-γ to drive keratinocyte activation and inflammatory amplification.[1,3,4]

Sex hormones play critical roles in modulating psoriasis, primarily through the IL-23/IL-17 signaling axis. Estrogens typically suppress Th17-driven inflammation, and their decline after menopause is associated with increased disease severity.[5,6] Prolactin, on the other hand, promotes keratinocyte proliferation and immune activation, contributing to disease progression. Notably, estrogen exhibits a dual role in psoriasis pathogenesis: it can alleviate inflammation by enhancing IL-10 production, suppressing T-cell activity, and improving skin barrier function, but may also exacerbate the disease by upregulating IL-22 and IL-23 expression and stimulating keratinocyte proliferation.[7,8] These findings underscore the complex, context-dependent effects of sex hormones and highlight their potential as modulators in psoriasis treatment strategies.

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While current treatments such as topical corticosteroids, phototherapy, and biologics targeting IL-17 or IL-23 have significantly improved patient outcomes,[9,10] many individuals remain refractory or experience relapse upon treatment discontinuation. Thus, a deeper understanding of novel immune cell subsets contributing to psoriatic inflammation is essential to refine therapeutic approaches.

Mucosal-associated invariant T (MAIT) cells are a distinct subset of innate-like T lymphocytes that play a critical role in mucosal immunity and antimicrobial defense. These cells are abundant in peripheral blood, liver, and barrier tissues such as the skin. In psoriasis, MAIT cells infiltrate lesional skin and produce IL-17A, although their abundance is relatively low compared to conventional Tc17 cells, suggesting they serve as amplifiers rather than primary drivers of inflammation. In atopic dermatitis (AD), peripheral MAIT cell frequencies decline, but activated subsets (eg, $CD38^+$ MAIT cells) increase and secrete TNF-α and Granzyme B, contributing to skin barrier dysfunction and chronic inflammation. In contrast, in wound healing, skin-resident MAIT cells display a tissue-repair transcriptional signature at steady state and migrate to injury sites via CXCR6/CXCL16 signaling. They secrete amphiregulin (Areg), promoting keratinocyte proliferation and re-epithelialization. These dual roles highlight the therapeutic potential of selectively modulating MAIT cell responses in skin diseases—attenuating their pathogenic function in chronic dermatoses such as psoriasis and AD, while harnessing their reparative capacity in contexts like wound healing.

Given this context, the present study aims to elucidate the transcriptional and metabolic landscape of MAIT cells in psoriatic skin using single-cell transcriptomics, and to explore potential regulatory genes involved in their activation. Through integrative analysis of scRNA-seq and eQTL datasets, we seek to uncover novel immune pathways and genetic factors that may contribute to disease progression and offer potential therapeutic targets for psoriasis management.

Materials and Methods

Data Acquisition and Selection for Single-Cell RNA Sequencing Analysis

Single-cell RNA sequencing data were obtained from the Gene Expression Omnibus (GEO) database under accession number GSE228421. The original dataset comprised full-thickness skin biopsies from five individuals with severe psoriasis. For the present analysis, we selected single-cell data from lesional skin of 3 psoriasis patients and non-lesional skin of 2 psoriasis patients.

Data Preprocessing, Normalization, and Clustering of Single-Cell RNA Sequencing Data

Cells with fewer than 200 detected genes or more than 10% mitochondrial gene content were excluded from the analysis. The remaining data were normalized using the LogNormalize method with a scale factor of 10,000. Highly variable genes were identified using the "vst" method, selecting the top 2,000 variable genes. These genes were then scaled, and principal component analysis (PCA) was performed. Batch effects were corrected using the Harmony algorithm, and clustering was conducted using the "FindClusters" function based on the first 10 principal components. Cell types were identified by applying the SingleR algorithm with reference to the Human Primary Cell Atlas. The metadata of the Seurat object were updated accordingly, and split UMAP plots were generated to visualize the distribution of cell types across different sample groups. A bar plot was used to visualize the relative proportions of various cell types in different samples.

Isolation and Annotation of Feature Cells

Data focusing on feature cells were isolated from the larger dataset. The isolated data underwent variable feature selection, scaling, and PCA. Harmony was then used to correct batch effects, followed by clustering and UMAP dimensionality reduction. The relative proportions of each feature cell subtype across different tissue types were displayed in a bar plot. Feature cell subtypes in psoriasis single-cell RNA sequencing data were identified using the SingleR package with MonacoImmuneData as a reference. The SingleR function assigned cell types to the feature cell subset (scRNAsub), and these annotations were set as the primary clustering labels in the Seurat object. Cell type distributions across different tissue types were visualized using DimPlot with custom color palettes. A bar plot was generated to show the proportions of each feature cell subtype in different samples.

Trajectory and Cell Communication Analysis of Feature Cells

We analyzed feature cell trajectories in scRNA_T using the Slingshot package, converting the data into a SingleCellExperiment object. Trajectories were inferred using UMAP, with feature cell types as cluster labels, originating from clusters 3 and 5. The UMAP plot of feature cell trajectories was overlaid with Slingshot lineage paths. Next, we assessed cell communication by merging non-feature cells with feature cell-specific data. A subset of 1,000 cells was randomly selected for analysis. Ligand-receptor interactions and overexpressed genes were identified using the CellChat package, with interaction networks visualized and bubble plots created for specific cell types.

Comparing Functional Pathways Between High and Low MAIT Cell Expression Groups in Psoriasis

Data Source

The present work acquired gene expression profiles in psoriasis and healthy samples in GEO database. GSE117239 dataset included altogether 324 samples, with 240 psoriasis and 84 healthy samples.

Comprehensive Analysis of MAIT Gene Expression and Functional Pathway Enrichment in Psoriasis Samples

We employed clustering analysis with ConsensusClusterPlus to classify psoriasis samples based on MAIT gene expression into high- and low-expression groups. PCA was conducted to explore sample distribution and clustering, using normalized MAIT-related gene data to retain variance. Differential gene expression analysis between C1 and C2 groups was performed using the limma package, identifying DEGs with FDR < 0.05. GO and KEGG enrichment analyses were applied to DEGs to investigate biological processes, molecular functions, cellular components, and pathways.

We applied the single-sample Gene Set Enrichment Analysis (ssGSEA) method to calculate enrichment scores for each sample across different pathways, using the GSVA package for analysis. Based on sample grouping information, enrichment scores were compared between the C1 and C2 groups, and boxplots were generated using the ggpubr package to visualize inter-group differences in functional enrichment scores.

Marker Genes eQTL Mendelian Randomization Analysis

eQTL Datasets

The discovery blood eQTL dataset was sourced from eQTLGen (https://eqtlgen.org/), containing cis-eQTLs for 16,987 genes derived from 31,684 blood samples of healthy individuals of European ancestry. Cis-eQTL results with full statistical significance (false discovery rate (FDR) < 0.05) and allele frequency data were included.[11]

Psoriasis GWAS Dataset

We utilized genome-wide association study (GWAS) summary statistics for psoriasis as outcome data in Mendelian randomization (MR) analysis. GWAS results from the Finnish database, including 4,510 psoriasis cases and 212,242 controls, covering a total of 16,380,464 SNPs, were employed. The validation set comes from a psoriasis dataset in the UK biobank, consisting of 5,314 psoriasis cases and 457,619 controls, covering a total of 9,851,867 SNPs.

Marker Gene Selection

First, the FindMarkers function was used to identify genes specifically upregulated in MAIT cells compared to other T cell subtypes. To ensure statistical significance, a logfc.threshold of 0.5 was set, meaning only genes with a log fold change greater than 0.5 were considered, and only positively regulated genes were retained. Similarly, specific upregulated genes in MAIT cells compared to other cell types (such as DC cells, monocytes, etc). were identified. The intersect function was then used to find common differentially expressed genes between these two datasets, which were defined as the final marker genes.

eQTL MR Analysis

MR analyses were performed using the R package TwoSampleMR V.0.5.6. eQTLs from the drug genome served as the exposure dataset. To construct instrumental variables (IVs), SNPs with a false discovery rate (FDR) <0.05 and within ±100 kb of each gene's transcription start site (TSS) were selected. These SNPs were subsequently clumped at an r^2 <0.01 using

European ancestry samples from the 1000 Genomes Project. The R package PhenoScanner V.1.0 identified phenotypes associated with the IVs. Outcome data were then loaded and harmonized through built-in functions. The Wald ratio method calculated MR estimates for individual SNPs, and, when multiple SNPs were available, a weighted average of the ratio estimates was derived, weighted by the inverse variance of the estimates (inverse-variance weighted, IVW).[12] To test for horizontal pleiotropy, the MR-Egger intercept was evaluated to see if it significantly differed from 0, provided there were at least three SNPs. Additionally, heterogeneity between Wald ratios was assessed with Cochran's Q test. FDR-adjusted p-values were calculated, with FDR <0.05 deemed significant. In replication studies, nominal p-values <0.05 were considered statistically significant.

Reverse MR Analysis

In the reverse MR analysis, instrumental variables for psoriasis were extracted and harmonized with outcome data related to a feature gene. Odds ratios were computed, and results were visualized in a forest plot, highlighting the genetic association with the feature gene.

Colocalization Analysis of eQTL and GWAS Data

To assess whether SNPs may share causal variants for psoriasis and gene expression, we performed colocalization analysis using the coloc package. We merged eQTL data and GWAS data based on SNP identifiers, removing duplicate SNP records. Colocalization analysis was conducted using the coloc.abf function. The input data for the analysis included p-values from eQTL and GWAS, as well as the MAF for each SNP. We set the following parameters: For GWAS data, we included p-values, sample size (N=216,752), and phenotype type (cc for case-control study). For eQTL data, we included p-values, sample size (N=5,329), and phenotype type (quant for continuous phenotype). Through colocalization analysis, we calculated the probability that each SNP shares causal variants for psoriasis and eQTL, represented by posterior probabilities (PP) for the following hypotheses: PPH0: The SNP has no association with any trait.PPH1: The SNP is linked to gene expression but not to psoriasis susceptibility.PPH2: The SNP is linked to psoriasis susceptibility but not to gene expression.PPH3: The SNP is associated with both psoriasis susceptibility and gene expression, although with distinct causal variants.PPH4: The SNP is associated with both psoriasis susceptibility and gene expression, sharing the same causal variants.[12,13]

Analysis of Marker Genes Expression in Different Cell Types

We analyzed the average expression levels and expression proportions of RPS10, RPS20, RPS29, and PFN1 in different cell types, obtaining the expression patterns of these genes in endothelial cells, monocytes, dendritic cells, T cells, and keratinocytes. Subsequently, we analyzed the differential expression of PFN1 between the psoriasis group and the control group across different cell types. Finally, we applied dimensionality reduction algorithms to analyze the distribution differences of PFN1 in various T cell subsets (such as natural killer cells, regulatory T cells, and Th17 cells) between the psoriasis group and the control group.

Communication Analysis of PFN1-Enriched (MAIT+) and PFN1-Depleted (MAIT-) Cell Subsets

MAIT cells were classified into PFN1-enriched (MAIT+) and PFN1-depleted (MAIT-) subsets based on PFN1 expression levels. Using CellChat, ligand-receptor interactions between different cell types or subsets were analyzed. CellChat quantified potential signaling pathways and molecular interactions from gene expression profiles, providing communication probabilities and statistical significance.

We subsequently extracted the transcriptomic data of different cell types and utilized CellChat to predict ligand-receptor interactions between cells. The intercellular communication networks were then visualized through network graphs, illustrating the communication relationships among various cell types.

Metabolic Pathways Analysis

Additionally, we assessed the metabolic activity of specific cell subpopulations with the scMetabolism package, focusing on KEGG pathways to explore metabolic differences within the psoriasis microenvironment.

Bulk RNA-Seq Validation

Download the psoriasis dataset GSE13355 from the GEO database, then proceed with data reading and processing. Perform Wilcoxon tests to assess the significance of expression levels of key genes between the control and psoriasis groups. Calculate the average expression values for each gene in both groups and compute the log fold change (logFC). Determine whether each gene is upregulated or downregulated based on logFC. Obtain statistical results for significant genes, including gene names, average expression values for control and treatment groups, p-values, and regulation types.

Result

Single-Cell Transcriptomic Profiling Reveals Immune and Structural Cell Shifts in Psoriasis

We performed single-cell RNA sequencing and identified five major cell types: keratinocytes, T cells, dendritic cells (DCs), monocytes, and endothelial cells. Compared to controls, psoriatic skin showed an increased abundance of T cells, DCs, keratinocytes, and monocytes, with a reduction in endothelial cells. This compositional shift reflects immune activation and structural remodeling in the psoriatic microenvironment (Figure 1A–F).

MAIT Cells Are Central Players Among T Cell Subsets in Psoriasis

We identified six major T cell subsets in both psoriatic and control samples: MAIT cells, regulatory T cells, non-Vd2 γδ T cells, Th17 cells, NK cells, and Vd2 γδ T cells. Among them, MAIT cells represented the most abundant population in psoriatic skin, suggesting their potential involvement in disease pathogenesis (Figure 2A–D).

Trajectory analysis revealed that MAIT cells and NK cells were located at the early developmental stages, while regulatory T cells resided at terminal differentiation positions. This pseudotemporal ordering indicated dynamic functional transitions among these subsets (Figure 2E).

We further analyzed intercellular communication patterns, focusing on MAIT cell interactions. MAIT cells showed robust crosstalk with Th17 cells and regulatory T cells. Two major signaling axes—CXCL12–CXCR4 and MIF–CD74 +CXCR4—were prominent in these interactions. Additionally, MAIT–monocyte interactions involved MIF–CD74 +CD44 signaling, while the TGFB1–TGFBR1/2 pathway showed relatively weak expression, implying suppression of TGF-β signaling (Figure 2F). These patterns collectively suggest that MAIT cells serve as a central immunoregulatory node in psoriatic inflammation.

MAIT Cell States Show Divergent Inflammatory and Metabolic Programs

Psoriatic MAIT cells were transcriptionally divided into two distinct subgroups. The MAIT-high subgroup exhibited marked enrichment of inflammatory and metabolic pathways, including IL6/JAK/STAT3, TNF-α/NF-κB, IL2/STAT5, and glycolysis, suggesting a pro-inflammatory and metabolically active phenotype. In contrast, the MAIT-low subgroup showed elevated expression of fatty acid metabolism and apoptosis-related genes (Figure 3A–L).

Functional enrichment analyses revealed that differentially expressed genes in the MAIT-high group were significantly associated with small GTPase signaling, supramolecular fiber organization, and ubiquitin-related activities. These genes localized to the vacuolar membrane, ubiquitin ligase complexes, and spindles. KEGG pathway analysis further identified enrichment in TNF signaling, Fc gamma R-mediated phagocytosis, endocytosis, and cell cycle regulation, underscoring the heightened immune responsiveness and proliferative potential of the MAIT-high population (Figure 3M and N).

Causal Inference Highlights PFN1 as a Risk Factor in Psoriasis

We identified several MAIT cell marker genes (Supplementary Table 1) and conducted Mendelian randomization using these markers as exposures and psoriasis GWAS data as outcomes. The RPS20 gene showed a significant suppressive

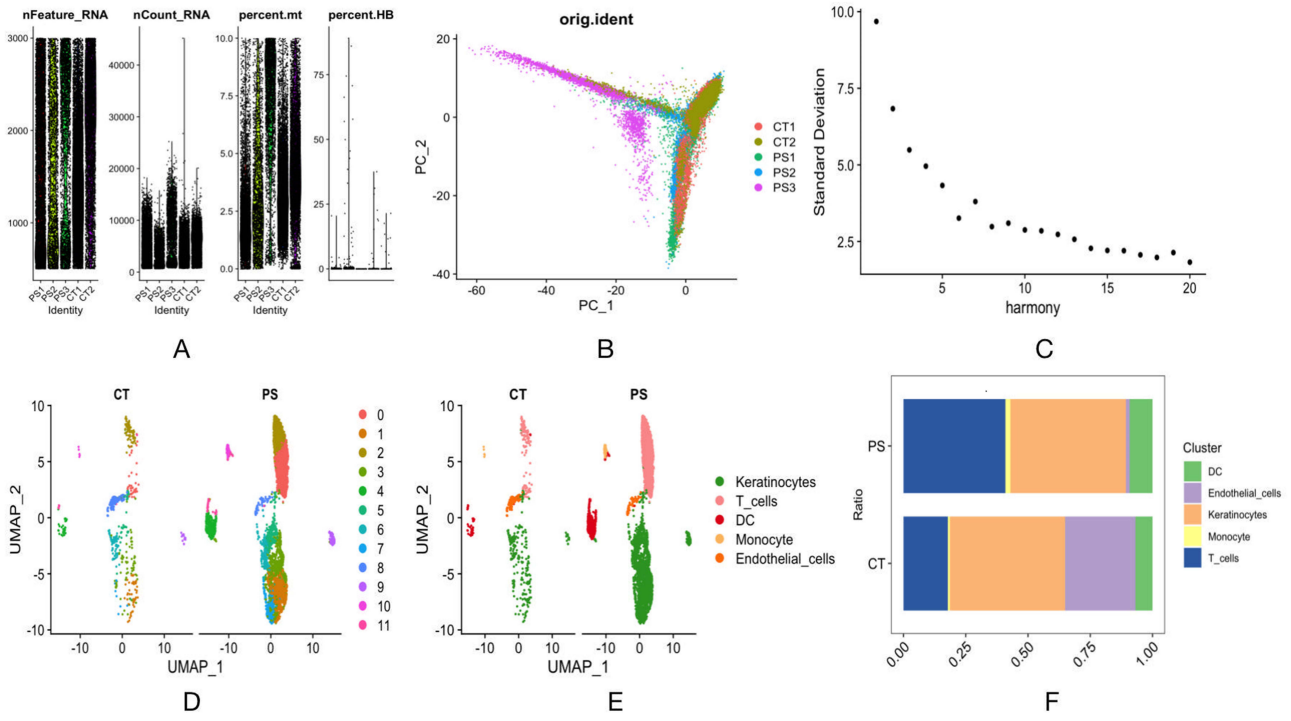


Figure 1 (**A**) UMAP plot displaying cell clustering results after quality control, showing distinct cell populations based on gene expression profiles. (**B**) Dimensionality reduction results after Harmony-based batch effect correction, distinguishing control (CT) and psoriasis (PS) groups. (**C**) Bar plot illustrating differences in cell type proportions between psoriasis and control groups, with distinct colors representing identified cell types. (**D**) UMAP plot depicting clustering of psoriasis single-cell data into 11 groups based on gene expression patterns. (**E**) Annotated UMAP plot identifying five major cell types. (**F**) Dot plot showing significant ligand-receptor interactions among cell types, with dot size representing statistical significance (p-value) and color indicating interaction probability.

effect on psoriasis, with a p-value of 0.011 (IVW method) and an OR of 0.5994 (95% CI: 0.40–0.89). In contrast, the PFN1 gene was associated with an increased risk of psoriasis, with a p-value of 0.037 (Wald Ratio method) and an OR of 1.7229 (95% CI: 1.03–2.88) (Figure 4A and B) (Supplementary Table 2). The validation set confirmed similar findings, supporting the reliability of these results (Figure 4C) (Supplementary Table 3).

PFN1 Does Not Exhibit Reverse Causality or Genetic Colocalization

Reverse Mendelian randomization analysis revealed no evidence supporting psoriasis as a causal factor for PFN1 expression, with all tested methods yielding non-significant p-values ($p > 0.05$) (Figure 4D, Supplementary Table 4).

Colocalization analysis showed a high posterior probability for the null hypothesis (PP.H0 = 0.9988), indicating no shared genetic variants between PFN1 expression and psoriasis risk. This lack of genetic overlap was further supported by minimal probabilities for alternative hypotheses, suggesting that PFN1 and psoriasis are regulated by distinct genetic mechanisms (Supplementary Table 5).

PFN1 Is Preferentially Expressed in MAIT and Non-Vd2 γδ T Cells

Analysis of key gene expression across different cell types showed high expression of PFN1 in DCs, T cells, and monocytes. RPS29 was highly expressed in T cells but showed low expression in monocytes (Figure 5A and B). Further analysis revealed significant enrichment of PFN1 in MAIT cells and non-Vd2 γδ T cells (Figure 5C).

PFN1^{+} MAIT Cells Coordinate Immune Signaling via CXCR4 and MIF Pathways

We found that PFN1+ MAIT cells exhibited significant communication intensity with other cell types, such as T regulatory cells and Th17 cells, through specific ligand-receptor pairs, including CXCL12-CXCR4 and (CD74 +CD44). Additionally, endothelial cells and dendritic cells (DC) also demonstrated strong communication associations, particularly through MIF-[CD74+CXCR4]. Furthermore, the cell communication network revealed that PFN1+ MAIT

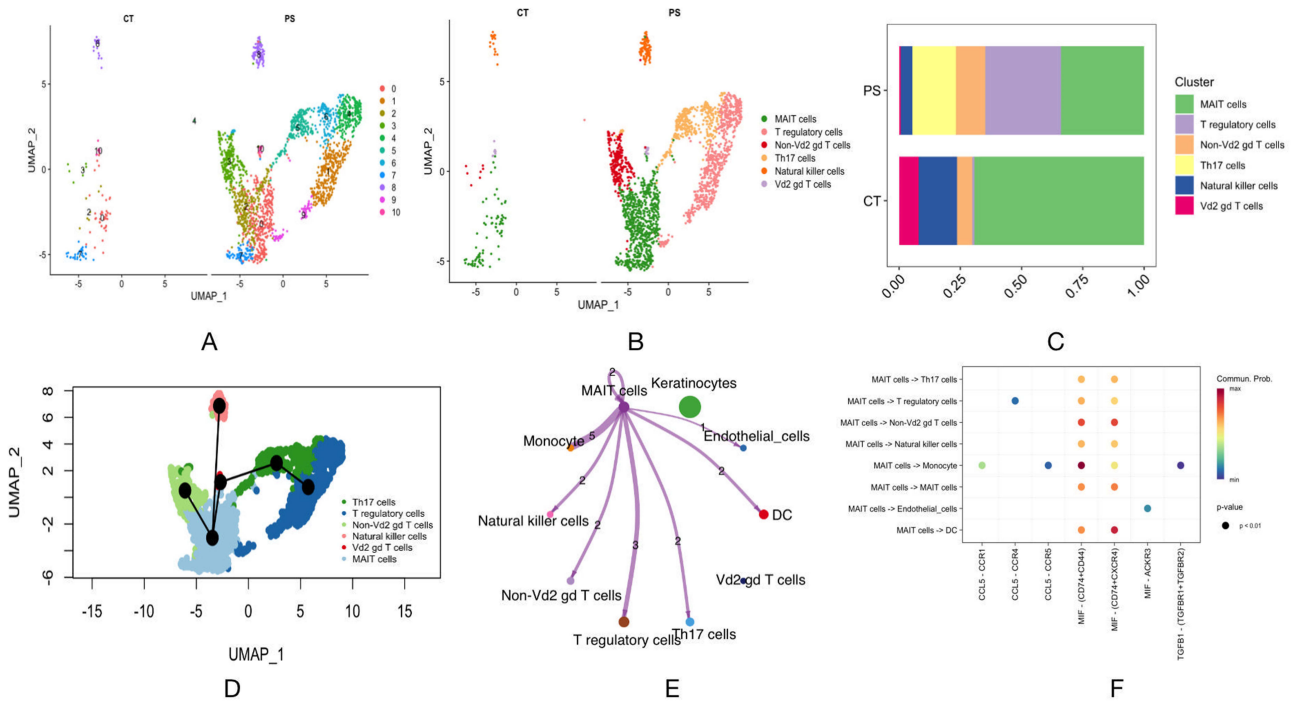


Figure 2 (**A** and **B**) The UMAP plot shows that T cells were clustered into 11 clusters after dimensionality reduction, and six T cell subsets were identified through cell annotation. (**C**) The bar plot displays the proportions of T cell subsets in psoriasis tissue and normal tissue, respectively. (**D**) In this UMAP plot, different colors represent different T cell subsets, and The Slingshot curves represent the developmental or transition pathways of cells. (**E**) The network diagram illustrates the interactions between different cell types, with the thickness of the edges and the intensity of the color representing the strength of the interactions. (**F**) The bubble plot of the interactions between MAIT cells and other cells.

cells formed close interactions with dendritic cells, endothelial cells, and natural killer cells, suggesting that these cells may collaboratively participate in regulating relevant biological processes (Figure 6A and B).

PFN1+ MAIT Cells Exhibit Distinct Metabolic Programs Among T Cell Subsets

PFN1^{+} MAIT cells were predominantly enriched in metabolic pathways associated with folate biosynthesis and xenobiotic degradation, including cytochrome P450 and glycosaminoglycan degradation. In contrast, PFN1^{-} MAIT cells were enriched in pathways such as retinol metabolism and glycosphingolipid biosynthesis. Other T cell subsets displayed distinct metabolic signatures: Th17 cells favored xenobiotic metabolism, Tregs were linked to one-carbon metabolism, NK cells with riboflavin metabolism, and Vd2 γδ T cells with CoA and nicotinate metabolism (Figure 6C).

PFN1 Expression Is Upregulated in Psoriatic Skin Tissues

Analysis of bulk RNA-seq data from GSE13355 revealed that PFN1 expression was significantly elevated in psoriatic lesions compared to healthy controls ($p = 5.80e{-}17$), corroborating single-cell and genetic evidence of its role in psoriasis pathogenesis (Supplementary Table 6).

Discussion

The present study integrates single-cell transcriptomics, Mendelian randomization, and functional pathway analyses to elucidate the role of mucosal-associated invariant T (MAIT) cells—particularly the PFN1-expressing subset—in the pathogenesis of psoriasis. Our findings establish MAIT cells as key orchestrators of psoriatic inflammation and uncover novel mechanistic insights with potential therapeutic implications.

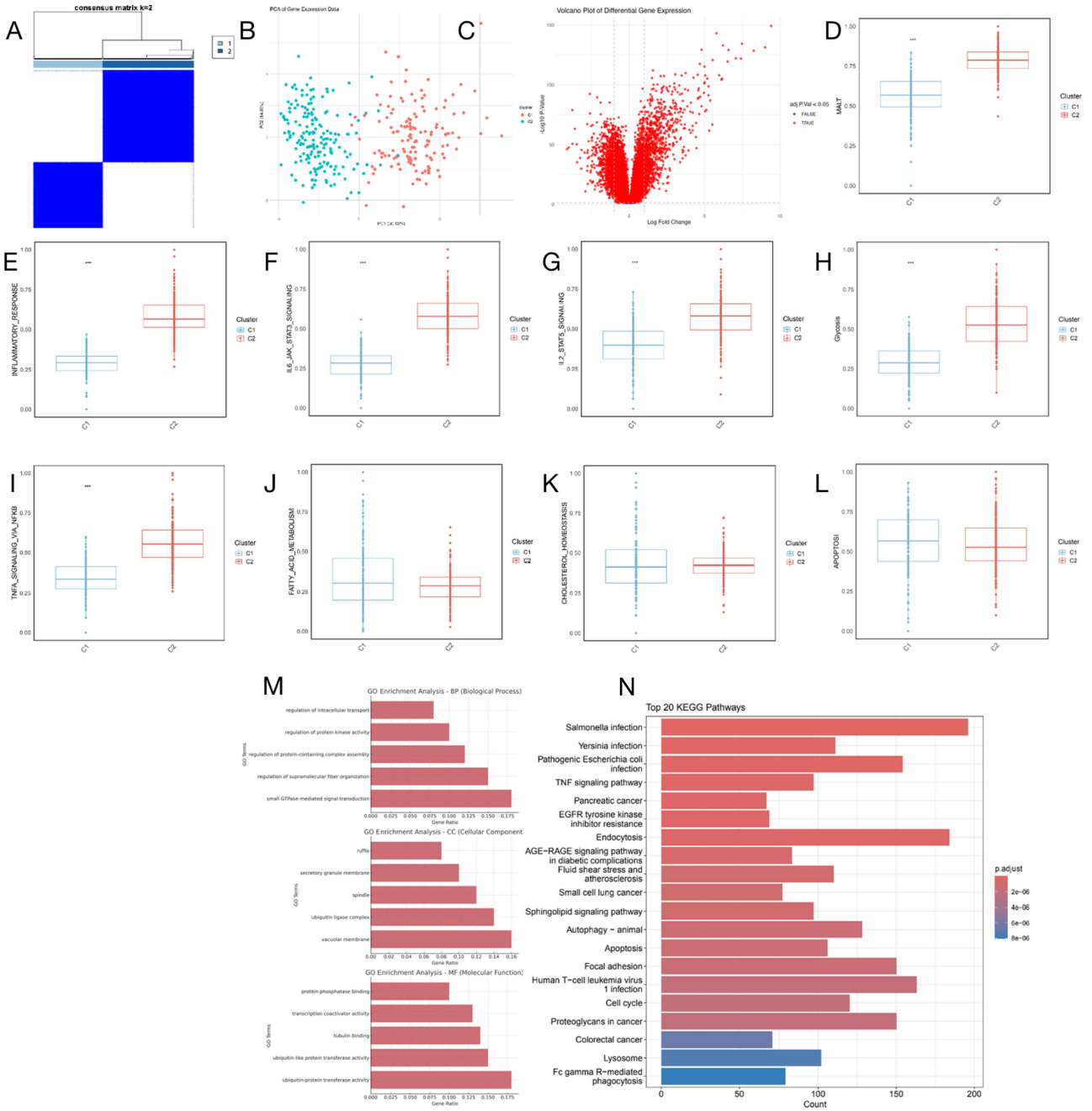
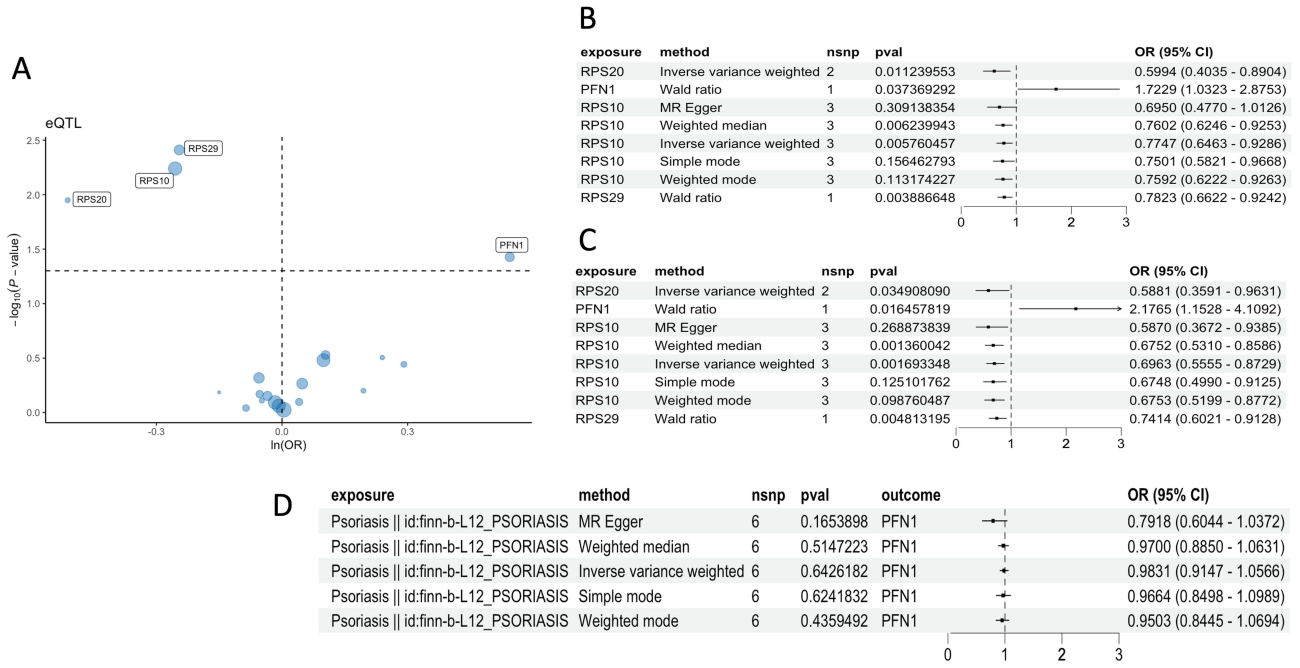


Figure 3 Transcriptomic and pathway differences between MAIT-low (C1) and MAIT-high (C2) expression groups in psoriasis. (**A**) Correlation heatmap based on the expression of MAIT cell–associated genes across samples in the psoriasis dataset. Hierarchical clustering reveals two distinct groups: C1 (MAIT-low group, marked in blue) and C2 (MAIT-high group, marked in red). Color intensity represents Pearson correlation coefficients (ranging from −1 to +1), with red indicating strong positive correlation and blue indicating strong negative correlation. (**B**) Principal component analysis (PCA) plot showing the distribution of individual samples in two-dimensional space based on overall gene expression profiles. Each dot represents a sample; red indicates C2 and blue indicates C1. PC1 and PC2 represent the top two principal components explaining the largest variance across samples. (**C**) Volcano plot of differentially expressed genes (DEGs) between C2 and C1 groups. Each dot represents one gene. Red dots indicate significantly upregulated genes in C2 (log2 fold change > 1, adjusted p-value < 0.05), blue dots indicate significantly downregulated genes (log2 fold change < −1, adjusted p-value < 0.05), and gray dots are non-significant (adjusted p-value ≥ 0.05). (**D–L**) Box plots showing the expression levels of selected DEGs between the C1 and C2 groups. Each box displays the median (center line), interquartile range (IQR; box edges), and 1.5× IQR (whiskers). Dots represent individual samples. Asterisks (*) denote statistical significance, with*** $p < 0.001$, as determined by the Wilcoxon rank-sum test. Genes displayed include representatives of immune regulation (eg, IL6, TNF), signaling pathways (eg, JAK/STAT, NF-κB), and metabolic regulators. (**M**) Gene Ontology (GO) enrichment analysis of DEGs classified into biological processes (BP), cellular components (CC), and molecular functions (MF). Bar length reflects the number of DEGs per GO term, and the color gradient (from dark red to light yellow) represents statistical significance (adjusted p-value). (**N**) KEGG pathway enrichment analysis showing the top 20 enriched signaling pathways among DEGs. Bar length represents the number of genes involved in each pathway; bar color indicates adjusted p-value (red = more significant, blue = less significant). Pathways such as TNF signaling, autophagy, and apoptosis are prominently enriched, suggesting that MAIT cell–related transcriptional states may drive psoriasis pathogenesis through these immunometabolic axes.



exposure	method	nsnp	pval	OR (95% CI)
RPS20	Inverse variance weighted	2	0.011239553	0.5994 (0.4035 - 0.8904)
PFN1	Wald ratio	1	0.037369292	1.7229 (1.0323 - 2.8753)
RPS10	MR Egger	3	0.309138354	0.6950 (0.4770 - 1.0126)
RPS10	Weighted median	3	0.006239943	0.7602 (0.6246 - 0.9253)
RPS10	Inverse variance weighted	3	0.005760457	0.7747 (0.6463 - 0.9286)
RPS10	Simple mode	3	0.156462793	0.7501 (0.5821 - 0.9668)
RPS10	Weighted mode	3	0.113174227	0.7592 (0.6222 - 0.9263)
RPS29	Wald ratio	1	0.003886648	0.7823 (0.6622 - 0.9242)

exposure	method	nsnp	pval	OR (95% CI)
RPS20	Inverse variance weighted	2	0.034908090	0.5881 (0.3591 - 0.9631)
PFN1	Wald ratio	1	0.016457819	2.1765 (1.1528 - 4.1092)
RPS10	MR Egger	3	0.268873839	0.5870 (0.3672 - 0.9385)
RPS10	Weighted median	3	0.001360042	0.6752 (0.5310 - 0.8586)
RPS10	Inverse variance weighted	3	0.001693348	0.6963 (0.5555 - 0.8729)
RPS10	Simple mode	3	0.125101762	0.6748 (0.4990 - 0.9125)
RPS10	Weighted mode	3	0.098760487	0.6753 (0.5199 - 0.8772)
RPS29	Wald ratio	1	0.004813195	0.7414 (0.6021 - 0.9128)

exposure	method	nsnp	pval	outcome	OR (95% CI)
Psoriasis || id:finn-b-L12_PSORIASIS	MR Egger	6	0.1653898	PFN1	0.7918 (0.6044 - 1.0372)
Psoriasis || id:finn-b-L12_PSORIASIS	Weighted median	6	0.5147223	PFN1	0.9700 (0.8850 - 1.0631)
Psoriasis || id:finn-b-L12_PSORIASIS	Inverse variance weighted	6	0.6426182	PFN1	0.9831 (0.9147 - 1.0566)
Psoriasis || id:finn-b-L12_PSORIASIS	Simple mode	6	0.6241832	PFN1	0.9664 (0.8498 - 1.0989)
Psoriasis || id:finn-b-L12_PSORIASIS	Weighted mode	6	0.4359492	PFN1	0.9503 (0.8445 - 1.0694)

Figure 4 (**A**) Volcano plots of the MR results. (**B**) MR Analysis results of marker genes and psoriasis risk. (**C**) External validation of the causal relationship between these four genes and psoriasis using data from the UK Biobank cohort through Mendelian randomization analysis. (**D**) Reverse Mendelian randomization results. (**B–D**) shows MR analysis using the Wald ratio, inverse variance weighted method, MR-Egger regression, weighted median, simple mode, or weighted mode on marker genes eQTL in relation to the risk of psoriasis.

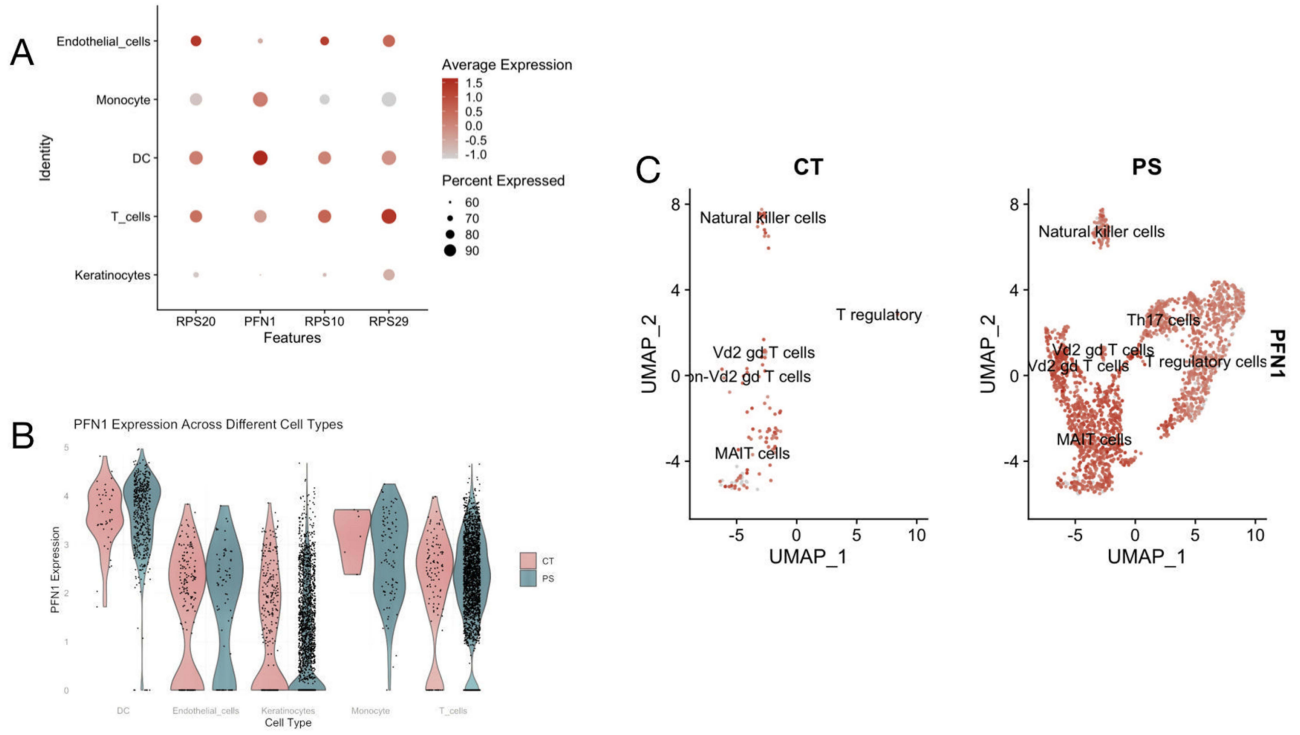


Figure 5 (**A**) Bubble plot showing the relationship between PFN1, RPS10, RPS20, RPS29, and various cell types. (**B**) Violin plot showing the relationship between PFN1 and various cell types. (**C**) The UMAP plot shows the expression of PFN1 in different T cell subtypes in psoriasis tissue compared to normal tissue.

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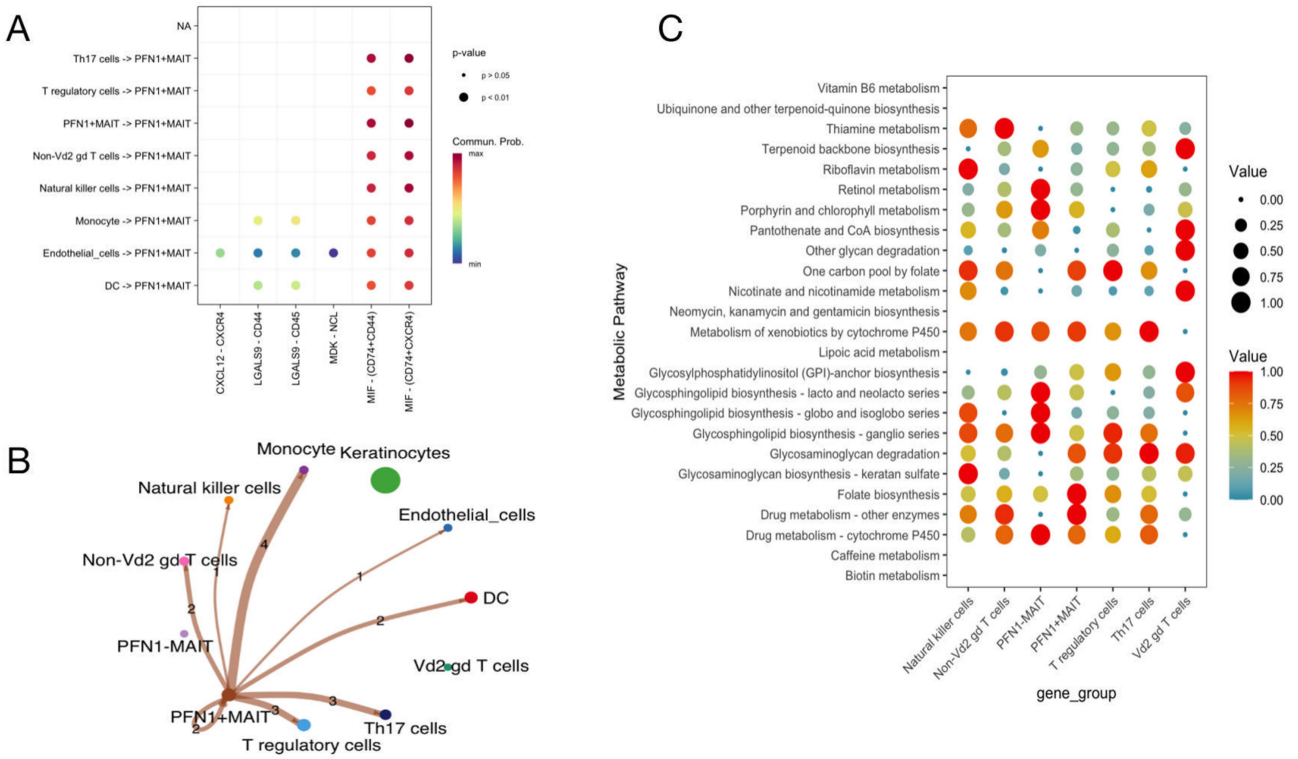

Figure 6 (**A**) The bubble plot shows the potential regulatory relationship between various cell types and PFN1+ MAIT cells. (**B**) The cell network diagram illustrates the cell-cell communication between PFN1+ MAIT cells and various other cell types. (**C**) The bubble plot shows the various metabolic pathways related to PFN1+ MAIT cells, PFN1- MAIT cells, and other T cell subtypes.

MAIT Cell Abundance and Early Activation

Single-cell RNA sequencing revealed an expansion of MAIT cells in psoriatic lesions, positioning them as the predominant T cell subset. This enrichment aligns with reports of elevated IL-17A–producing MAIT cells in psoriatic skin and synovial fluid, underscoring their tissue-specific accumulation and pro-inflammatory function.[14] Early investigations by Teunissen et al initially suggested that MAIT cells were unlikely to play a major role in psoriasis pathogenesis, as they were not increased in abundance compared to normal skin.[15] However, their subsequent work demonstrated that IL-17A–producing CD8+ MAIT cells were predominantly found in psoriatic lesional skin, suggesting a functional rather than numerical contribution to disease pathogenesis23. This apparent discrepancy highlights the importance of assessing MAIT cell activation state rather than mere presence, as we have observed in our trajectory analysis.

Trajectory analysis placed MAIT and NK cells at early pseudotime stages—contrasting with terminal differentiation of regulatory T cells—suggesting that MAIT cells act as early initiators of immune activation rather than downstream effectors. This positioning is supported by their rapid effector function capacity and glycogen-dependent metabolism that enables immediate cytokine production and cytotoxicity.[16,17] The early pseudotime positioning of MAIT cells in psoriatic lesions suggests they may participate in the initial phases of immune activation and cellular recruitment, supporting their role as “first responders” in the inflammatory cascade.

Intercellular communication mapping identified MAIT cells as hubs within pro-inflammatory networks, notably engaging Th17 and Treg cells via the CXCL12–CXCR4 and MIF–CD74–CXCR4 axes. This central positioning in communication networks provides mechanistic support for their role in orchestrating broader immune responses. The preferential expression of CXCR4 by MAIT cells in psoriatic lesions aligns with studies demonstrating enhanced tissue infiltration capacity and sustained inflammatory function.[18,19]

PFN1 as a Mechanistic Bridge

Mendelian randomization pinpointed PFN1 as a causal risk gene in psoriasis, with preferential expression in MAIT cells. PFN1 encodes profilin-1, a regulator of actin polymerization critical for cytoskeletal remodeling and immune synapse formation.[20] Kim et al demonstrated PFN1's role in modulating NF-κB signaling via IκBζ suppression, suggesting a dual anti-inflammatory and motility-enhancing function.[20] Our data extend these findings by implicating PFN1 in CXCR4-mediated endothelial transmigration and immunovascular remodeling within psoriatic lesions.

The cytoskeletal regulatory mechanisms mediated by PFN1 are particularly relevant to MAIT cell function. PFN1 regulates actin polymerization in response to extracellular signals and is essential for cellular motility and immune synapse formation.[21] In keratinocytes, PFN1 plays crucial roles in DNA damage response and repair machinery, with depletion leading to accelerated apoptosis and disrupted cell-cell adhesion.[21] The preferential expression of PFN1 in psoriatic MAIT cells suggests enhanced capacity for tissue infiltration and sustained inflammatory function.

Furthermore, PFN1's involvement in wound healing and endothelial cell migration provides additional mechanistic insight into its role in psoriatic pathogenesis12. The connection between wound healing and psoriatic plaques has long been recognized through the Koebner phenomenon, and PFN1 may serve as a molecular link between tissue repair mechanisms and chronic inflammation. The enhanced endothelial transmigration capacity of PFN1+ MAIT cells likely contributes to their accumulation in inflamed tissues and their ability to maintain chronic inflammatory responses.

Metabolic Heterogeneity Within MAIT Cells

We identified two metabolically distinct MAIT subpopulations: a MAIT-high subset characterized by upregulation of glycolytic pathways (IL6/JAK/STAT3, TNF-α/NF-κB, IL2/STAT5) and a MAIT-low subset enriched for fatty acid oxidation and apoptotic pathways. This dichotomy parallels single-cell analyses of psoriatic CD8+ T cells demonstrating metabolic reprogramming toward glycolysis in effector subsets.[22,23] The metabolic heterogeneity within MAIT cells reflects their functional plasticity and adaptation to different tissue environments and inflammatory contexts.

Glycolytic reprogramming in MAIT-high cells is supported by extensive evidence demonstrating the critical role of glucose metabolism in MAIT cell effector function. Studies have shown that MAIT cells preferentially upregulate glycolytic activity upon stimulation, with this upregulation accompanied by enhanced expression of effector molecules such as granzyme B.[16] The dependence on glycolysis for MAIT cell cytokine production, particularly IFN-γ, has been consistently demonstrated across multiple studies.[24] Inhibition of glycolysis using 2-deoxy-glucose severely limits MAIT cell effector function, highlighting the metabolic basis of their inflammatory capacity.

The MAIT-low subset's enrichment for fatty acid oxidation pathways aligns with the metabolic profile typically associated with regulatory and memory T cell populations.[25,26] Fatty acid oxidation has been traditionally linked to the development of CD8+ T cell memory and regulatory T cell differentiation.[27,28] However, recent evidence suggests that the relationship between fatty acid metabolism and immune cell function is more complex than previously understood. The metabolic quiescence of MAIT-low cells may represent a regulatory phenotype or a state of metabolic adaptation to chronic inflammation.

Recent studies have identified additional metabolic pathways supporting MAIT cell function. Glycogen metabolism has emerged as a critical pathway for rapid MAIT cell responses, with glycogen-fueled metabolism supporting both cytotoxicity and early cytokine production.[17] This metabolic pathway is particularly relevant for rapid effector responses that occur before glucose uptake and glycolysis can be fully activated. The ability of MAIT cells to store and metabolize glycogen provides them with the capacity for immediate effector function upon activation.

CXCR4 Signaling: Mechanistic Validation

Our identification of CXCR4-mediated signaling as central to MAIT cell function finds strong mechanistic support in the literature. CXCR4 plays an unexpected role in inhibiting keratinocyte proliferation and mitigating the effects of proliferative Th17 cytokines.[29] Studies have demonstrated that CXCR4 deficiency in keratinocytes results in exaggerated responses to IL-23, with increased epidermal thickness and enhanced inflammation.[29] The upregulation of CXCR4 in the junctional regions of psoriatic lesions suggests its role as a regulatory checkpoint in inflammation resolution.

The MIF-CD74-CXCR4 signaling axis represents a critical mechanistic pathway for MAIT cell function. MIF promotes cell migration and activation through heteromeric complexes formed between CD74 and CXCR4.[30] These complexes mediate MIF-specific signaling that is distinct from CXCL12-induced activation, providing specificity for inflammatory versus homeostatic responses. The formation of functional CD74/CXCR4 heterocomplexes on activated immune cells provides a mechanism for targeted therapeutic intervention.

The immunovascular interactions mediated by CXCR4 signaling are particularly relevant to psoriatic pathogenesis. CXCR4 expression on endothelial cells and its role in angiogenesis contribute to the vascular remodeling observed in psoriatic lesions8. The ability of MAIT cells to utilize CXCR4-mediated signaling for both tissue infiltration and interaction with endothelial cells positions them as key mediators of immunovascular crosstalk in chronic inflammation.

Ribosomal Stress and Psoriatic Pathology

Our observation of dysregulated RPS10, RPS20, and RPS29 expression implicates ribosomal stress as a novel contributor to both immune cell activation and keratinocyte dysfunction. Ribosomal protein RPS20 (uS10) is an indispensable constituent of the human ribosome, located in the head of the 40S ribosomal subunit where it contacts other ribosomal proteins and extends toward the mRNA-binding channel.[31] RPS20 belongs to a group of ribosomal proteins whose depletion results in defects in 18S rRNA maturation and decreased levels of mature 40S ribosomal subunits.

Recent studies have identified ribosome biogenesis as a critical pathway in psoriasis pathogenesis. Novel ribosome biogenesis-related biomarkers have been identified in psoriasis, with proteins such as MPHOSPH6 and ISG20 showing elevated expression in psoriatic lesions.[32] These findings suggest that ribosomal stress may serve as a unifying mechanism linking genetic susceptibility to tissue-specific pathology. The dysregulation of ribosomal proteins can trigger p53 pathway activation and pro-inflammatory cytokine release, both prominent features of psoriatic skin pathology.

The connection between ribosomal stress and immune cell function extends beyond simple protein synthesis regulation. Ribosomal proteins are involved in ribosome-associated quality control pathways, which recognize and degrade aberrant mRNAs and peptides.[31] The dysregulation of these quality control mechanisms may contribute to the sustained inflammatory responses observed in psoriasis. Furthermore, ribosomal stress can influence translation selectivity, potentially affecting the expression of specific inflammatory mediators and immune regulatory proteins.

Therapeutic Implications

The identification of MAIT cells as central orchestrators of psoriatic inflammation opens new therapeutic avenues. Current therapeutic approaches targeting the IL-23/IL-17 axis have achieved significant success but show variable response rates, highlighting the need for additional therapeutic targets.[23] Our findings suggest that MAIT cell-targeted therapies could provide synergistic benefits, particularly for patients with inadequate responses to existing biologics.

The development of precision medicine approaches for psoriasis requires robust biomarkers that can predict treatment response and guide therapeutic selection.[33,34] Our identification of PFN1 as both a causal risk gene and a functional protein suggests its potential as a diagnostic biomarker and therapeutic target. The metabolic dichotomy within MAIT cells provides additional stratification opportunities, as patients with predominant MAIT-high versus MAIT-low phenotypes may benefit from different therapeutic strategies.

MR1-blocking ligands represent a promising therapeutic approach for modulating MAIT cell function. Compounds such as DB28 and NV18.1 have been shown to down-regulate MR1 cell surface expression and inhibit MAIT cell activation.[35] These findings provide proof-of-concept for small molecule inhibitors that could selectively target MAIT cells without affecting conventional T cell responses. The development of such targeted therapies could provide precise immunomodulation with reduced systemic effects.

The integration of metabolic targeting with immunomodulation represents an innovative therapeutic approach. Given the dependence of MAIT-high cells on glycolytic metabolism, selective inhibition of glycolytic pathways could provide therapeutic benefits while preserving other immune functions.[36] Similarly, the targeting of ribosomal stress pathways could address both immune dysfunction and keratinocyte abnormalities simultaneously, providing a unified therapeutic approach to psoriatic pathogenesis.

Limitations and Future Directions

This study has several limitations. Most notably, the single-cell RNA sequencing sample size was relatively small, potentially limiting statistical power, the detection of rare cell subsets, and generalizability of the findings. Validation using larger and more diverse patient cohorts will be necessary to confirm these results. Furthermore, the dualistic function of MAIT cells—exhibiting both pro-inflammatory and potentially regulatory roles—reflects context-dependent complexity that requires deeper phenotypic and functional characterization. Metabolic interventions indicated by our data, such as glycolysis or fatty acid oxidation targeting, must be carefully evaluated for effects across different immune cell populations to avoid unintended consequences. Future studies should expand single-cell datasets across a broader clinical spectrum, further explore PFN1's role in MAIT cell motility and immune synapse formation and validate metabolic and ribosomal stress signatures in independent cohorts. These refinements are essential for translating our findings into clinically applicable interventions for psoriasis.

Conclusion

This study identifies MAIT cells and the actin-binding protein PFN1 as likely contributors to the pathogenesis of psoriasis. By integrating single-cell transcriptomic profiling, intercellular communication mapping, metabolic pathway analysis, and Mendelian randomization, we reveal that MAIT cells undergo distinct functional and metabolic polarization in the psoriatic microenvironment. PFN1 expression in MAIT cells is associated with enhanced immune signaling, increased cellular motility, and pro-inflammatory metabolic programs. These findings not only elucidate a novel immunometabolic mechanism in psoriasis but also propose PFN1+ MAIT cells as potential therapeutic targets and biomarkers. Future investigations should focus on validating the pathogenic role of PFN1 in vivo and assessing the therapeutic efficacy of MAIT cell-modulating strategies in clinical settings.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are available in the following locations: the scRNA-seq dataset was form the GEO dataset: https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE228421. The scRNA data for psoriasis was from the GEO dataset:The gene expression data for psoriasis and normal samples were obtained from the GEO dataset: https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE13355. The discovery blood eQTL dataset was obtained from eQTLGen (https://eqtlgen.org/). The summary statistics of GWAS data from the UK Biobank can be found at https://www.ukbiobank.ac.uk/. The summary statistics of GWAS data from FinnGen are accessible through https://www.finngen.fi/en.

Ethics Statement

This study utilized publicly available, de-identified single-cell transcriptomic data (GSE228421). According to Article 32 (items 1 and 2) of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (February 18, 2023, China), this reanalysis of anonymized data is exempt from additional institutional review board (IRB) approval.

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 declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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