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ORIGINAL RESEARCH

Integrated Single-Cell and Spatial Transcriptomic Analysis Reveals a Pathological Niche Formed by FAP+ Fibroblasts, Immune, and Endothelial Cells in Psoriatic Lesions

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Purpose: The dysregulated immune microenvironment represents a key pathogenic driver in psoriatic lesions. However, the intricate cellular and molecular interactions underlying psoriasis remain incompletely elucidated. Therefore, we aim to employ integrated multi-omics approaches to characterize the immune microenvironment and pathogenic niche in psoriasis, thereby elucidating the cellular and molecular mechanisms of disease pathogenesis.

Methods: Integrated Single-cell RNA sequencing (scRNA-seq), spatial transcriptomics, and bulk RNA sequencing (RNA-seq) data to explore the heterogeneity of stromal cells and immune cells in psoriatic lesions and the complex spatial niches formed between them. Enrichment analysis, intercellular communication analysis, and spatial co-localization analysis were used to investigate the transcriptional changes and distribution characteristics of each cell type in the lesions of psoriasis patients.

Results: Using scRNA-seq, we identified a novel CD4+ tissue-resident memory T cell (TRM) subset that is exclusively present in lesional skin of psoriasis patients but absent in healthy skin. These cells exhibit elevated expression of genes including IL17RA, IL22, PD1 (PDCD1), CXCR6, ITGAE, CD69, TNFRSF9, TNFRSF4, IL7R, CD4, and STAT3. Additionally, we discovered a novel microvascular endothelial cell subset, designated Venous endo2, which highly expresses CD93, ACKR1, ICAM1, VCAM1, IL15, SELE, and SELP, while also overlapping with high endothelial venule (HEV)-associated transcriptional signatures. Integrated analysis of scRNA-seq and spatial transcriptomics further revealed strong spatial co-localization of Venous endo2 with fibroblast activation protein-positive fibroblasts (FAP+ Fbs), T cells, and antigen-presenting cells (APCs) in Psoriasis lesions—a pattern not observed in healthy control skin.

Conclusion: Through integrated multi-omics analysis, we identified a potential pathogenic niche in psoriasis patients, composed of Venous endo2, FAP+ Fbs, T cells, and APCs. This structure resembles tertiary lymphoid structures (TLS), suggesting a functional parallel in disease pathogenesis.

Keywords: psoriasis, single-cell RNA sequencing, spatial transcriptomics, immune microenvironment, inflammatory skin disease

Introduction

Psoriasis is a common chronic inflammatory skin disorder characterized by a prolonged course and high recurrence rates, significantly impacting the physical and mental health of patients. Globally, over 125 million individuals are affected by psoriasis, with nearly one-quarter of patients experiencing moderate to severe forms of the disease.[1] The abnormal

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immune microenvironment serves as a key pathogenic factor in the development of psoriasis. Interactions between immune cells and stromal cells within the psoriatic skin microenvironment are mediated by cytokines, including TNF-α, IFN-γ, IL-17, IL-22, and IL-23. These interactions drive a self-sustaining inflammatory cycle.[2–4] Although numerous therapeutic strategies targeting the immune features of psoriasis have emerged—including biologics directed at the IL-23/IL-17 pathway—leading to unprecedented success in treatment, many patients with moderate-to-severe psoriasis still experience diminished drug efficacy and relapse during therapy.[5] This underscores the imperative to further dissect the disease's heterogeneity and explore novel therapeutic targets.[6] Unraveling the intricate molecular signaling networks and disease-driving pathological niches within the psoriatic immune microenvironment remains a formidable challenge. Single-cell RNA sequencing (scRNA-seq) has transformed our understanding of the psoriatic immune microenvironment through its unprecedented cellular-resolution profiling. Cutting-edge research employing this technology has decoded the cellular landscape of psoriatic lesions via multiple analytical dimensions: cross-disease comparisons (particularly with atopic dermatitis), comprehensive profiling of heterogeneous cellular states (including fibroblasts, keratinocytes, T/B lymphocytes, and macrophages), dynamic reconstruction of cell-cell communication networks, and longitudinal monitoring of treatment-induced transcriptional reprogramming in psoriatic lesions.[7–11] However a major limitation of scRNA-seq lies in its loss of spatial information, which is a critical dimension for understanding tissue pathophysiology. Spatial transcriptomics emerges as a transformative solution to address this gap by simultaneously mapping disease-driven pathological niches and characterizing dysregulated cell-cell communication networks within these distinct tissue compartments. Thus, integrating both approaches enables a more comprehensive analysis of the heterogeneity in psoriasis lesional skin.[12–14] Recently, a novel structure known as inductive skin-associated lymphoid tissue (iSALT) has been defined in mice, which is composed of postcapillary venules, T cells, dendritic cells(DCs), and other cellular components.[15] This structure is similar to tertiary lymphoid structures (TLS). Which are detectable in non-lymphoid tissues of patients with conditions such as infections, chronic inflammation, or cancer.[16] The characteristics of TLS include the presence of distinct T cell and B cell areas, peripheral lymph node addressins, high endothelial venules (HEVs), a lymphatic vessel system, and B cell class switching.[17] iSALT is considered a structure analogous to TLS in the skin have been observed.[18] However, current research has not adequately interpreted the cellular composition and function of these structures in psoriasis lesions.[18] Here, through integrated multi-omics analysis, we deciphered the cellular composition and transcriptional features of an iSALT-like structure in psoriasis. Our findings reveal that T cells, antigen-presenting cells (APCs), venous endothelial cells, and fibroblasts collectively form a pathological niche capable of recruiting and activating T cells. This niche facilitates the aggregation of APCs and T cells, amplifies localized immune responses, and likely exacerbates psoriatic inflammation by orchestrating psoriasis-associated inflammatory signaling pathways. Critically, this structure may contribute to the maintenance of immune memory in psoriatic skin, enabling rapid immune reactivation upon re-exposure to stimuli. Such sustained immune memory could underlie the chronic recurrence of psoriasis. We therefore propose that this niche plays a pivotal role in the pathogenesis of psoriasis. In addition, we identified different immune cell and stromal subpopulations in the lesions of psoriasis patients and analyzed the key intracellular transcription factors associated with these cells. Through the integration of spatial transcriptomics and single-cell data analysis, we also examined the spatial distribution of TNF-α, JAK-STAT, and NF-κB signaling pathway activity within psoriasis lesions, as well as their positional relationships with various cell types. This study investigated the molecular and cellular mechanisms underlying the pathogenesis of psoriasis by analyzing the subpopulations, spatial distribution, and functional characteristics of key immune and stromal cells within the lesions of psoriasis patients.

Materials and Methods

Identification of Various Omics Datasets

We systematically searched the Gene Expression Omnibus (GEO) for transcriptomic datasets from psoriasis patients and healthy controls, including datasets from human microarray chips and RNA sequencing. Additionally, we identified scRNA-seq datasets and spatial transcriptomics datasets from both psoriasis patients and healthy controls for further analysis. The inclusion criteria for single-cell transcriptomic and bulk transcriptomic data from skin tissues were as

follows: (1) the case group consisted of patients with plaque psoriasis, while the control group comprised healthy individuals; (2) bulk transcriptomic datasets were sequenced using RNA-seq; (3) each dataset included a minimum of three samples per group. Ultimately, we included the RNA sequencing dataset GSE121212 and the single-cell psoriasis skin dataset GSE162183.

The selection criteria for the spatial transcriptomic dataset of skin tissues that we employed included the following: (1) the case group consisted of patients with plaque psoriasis, while the control group comprised healthy skin; (2) the dataset was generated using the 10x Visium spatial transcriptomics technology platform from 10X Genomics.

scRNA-Seq Analysis

We utilized the R package Seurat (version 4.2) to conduct the analysis of the scRNA-seq data.[19] Cells with more than 800 feature genes and a mitochondrial gene percentage of less than 10% were considered high-quality cells and included in subsequent analyses. During the integration of multi-sample single-cell data, batch effects inevitably arise, which can confound differences with biological variations. To eliminate these batch effects, we utilized the Sctransform function in Seurat to integrate scRNA-seq data from different samples. We selected the top 3000 highly variable genes for downstream analysis.

For the integrated single-cell data, we conducted principal component analysis (PCA), a commonly used method for multivariate data reduction and visualization. PCA transforms the original high-dimensional data into a lower-dimensional principal component space through linear transformation. We chose 30 principal components (PCs) for further dimensionality reduction and clustering. Subsequently, we employed Seurat's FindClusters function to cluster the cells. To visualize the integrated single-cell data, we applied Uniform Manifold Approximation and Projection (UMAP) and t-Distributed Stochastic Neighbor Embedding (t-SNE) for dimensionality reduction and represented the data in a two-dimensional space.[20]

Integration Analysis of scRNA-Seq and Spatial Transcriptomics

Due to the limitations of the 10X Visium technology, each spot in the spatial transcriptomics is sized at 55μm × 55μm, potentially containing anywhere from a few to dozens of cells. To achieve precise cellular localization in space, we utilized Cell2location to calculate the cellular composition at each spot in the spatial transcriptomics dataset. By employing regularized negative binomial regression alongside our integrated scRNA-seq data, we constructed reference expression signatures of major cell types.

After obtaining reference signatures from the scRNA-seq data for deconvolution, Cell2location provided the absolute abundance of cell types at each spot in the spatial transcriptomics, reflecting the distribution density of different cell types. We used the default parameters for the analysis, except for the cells_per_spot parameter, which was set to 20. Each spatial transcriptomics dataset was analyzed individually. The results were then visualized following the Cell2location tutorial.[21,22]

Co-Localization Analysis of Cell Types in Spatial Transcriptomics and Pathway Signaling Activity Analysis

After obtaining the cell distribution density matrix for each spot in the spatial transcriptomics, we utilized MISTy to perform co-localization analysis of the major cell types. The importance values were interpreted as the dependence of cell types in different spatial environments, such as co-localization or mutual exclusion.[22,23]

For each spot, we standardized the spatial transcriptomics data using Sctransform and subsequently assessed the pathway activity of the spatial transcriptomics data through the PROGENy model matrix,[24,25] and conducted co-localization analyses of the signaling pathway relationships with different cell types.

Analysis of Transcription Factors

To understand the differences between cell subpopulations in the skin of psoriasis patients and healthy controls, as well as the underlying pathological drivers, we employed the Single-cell Regulatory Network Inference and Clustering (SCENIC) method to analyze the transcription factor differences among various cell subpopulations in the skin of

patients and healthy controls. This approach first utilizes GENIE3 to infer gene co-expression networks. Given that the co-expression modules inferred by GENIE3 may contain many indirect targets, we subsequently performed cis-regulatory motif analysis using RcisTarget on each co-expression module to eliminate these indirect targets. Each transcription factor (TF) and its potential direct target genes are referred to as a regulon. The AUCell algorithm was employed to score the activity of each regulon in every cell, ultimately generating a binary matrix that displays the "switch" status of the genes.[26] Recently, a new method was developed to quantify the specificity of regulons across different cell types, known as the Regulon Specificity Score (RSS). The RSS provides a better representation of the specificity of transcription factors in cells.[27]

Gene Set Variation Analysis

Gene set variation analysis (GSVA) is a method for analyzing biological information from RNA sequencing data at the single-sample level.[28] It can be used to infer the activity levels of gene sets/pathways in individual samples. The main steps are as follows: (1) Define gene sets: Select one or more gene sets of interest, which can be predefined pathways, functional modules, or other collections of genes. Common sources for gene sets include public databases (such as MSigDB) or custom gene sets. The gene sets we defined are derived from differentially expressed genes obtained from single-cell sequencing of cell types.(2) Activity calculation: For each sample, GSVA computes the activity score of gene sets by calculating the cumulative distribution function (CDF) of the genes within the gene set. (3) Score matrix: The activity scores of gene sets calculated for each sample are compiled into a matrix, where the rows represent gene sets and the columns represent samples. This score matrix can be used for further analysis and visualization. The advantage of GSVA is that it provides quantitative information on the activity levels based on entire gene sets, rather than focusing solely on the expression of individual genes. It can reveal functional differences between samples and help identify gene sets that play significant roles in biological processes and disease progression. When performing GSVA analysis using the GSVA package, all parameters were set to their default values.

Gene Ontology Enrichment Analysis

Gene ontology enrichment analysis (GO enrichment analysis) determines which functions or processes are significantly represented in a given gene set by comparing the genes within that set to predefined functional annotations in the Gene Ontology (GO). The Gene Ontology is a hierarchical structure that categorizes gene functions into three main aspects: Molecular Function (MF), Biological Process (BP), and Cellular Component (CC). It is used to describe the functions of genes, the biological processes they are involved in, and the cellular components where they are located. During the enrichment analysis, we employed the Benjamini-Hochberg method to estimate the significance of signaling pathways. Pathways meeting the criteria of p-value cutoff = 0.05 and q-value cutoff = 0.25 were identified as significantly enriched.[29]

Immunofluorescence Staining Was Performed on Paraffin-Embedded Skin Sections Obtained from Psoriasis Patients

Details of antibodies and instruments for immunofluorescence staining are provided in the Supplementary Materials.

Results

ScRNA-Seq Analysis Reveals the Cellular Composition of the Immune Microenvironment in the Skin of Psoriasis Patients

Our study included scRNA-seq data from the skin of three patients with plaque psoriasis (psoriasis group) and three healthy controls (healthy control group). After quality control processes toremove cells with more than 10% mitochondrial content and doublets, a total of 11,689 high-quality cells were obtained for downstream analysis. Through dimensionality reduction, we divided these cells into 19 clusters. To identify the cell types within each cluster, we utilized the FindAllMarkers function in Seurat to compare the expression profiles of cells in that cluster with those of other cells. The differential expression analysis implemented in this function used the default two-sided, non parametric

Wilcoxon rank-sum test to compare gene expression differences between the cells in that cluster and those in all other cell clusters. If the Bonferroni-adjusted p-value is below 0.05, and the average natural logarithm fold change (LogFc) in expression is greater than 0.25 with at least 10% of cells in the cluster expressing the gene, it is classified as a significantly differentially expressed gene. By analyzing the expression of differential genes, we identified marker genes for each cell type and annotated the cell populations. In the annotation process, we referenced the results from SingleR as well as expression genes of various skin cell types reported in published literature.[30] The criteria for selecting marker genes include: (1) being ranked among the top differentially expressed genes in the corresponding cell cluster; (2) having strong expression specificity, meaning a high expression rate within the respective cell cluster and a low expression rate in other cell clusters; (3) being supported by literature, indicating that the gene is either a marker gene or a functionally relevant gene associated with the cell type. The FindAllMarkers function can also perform differential gene analysis between any two cell clusters, both within and between groups. As shown in Figure 1A and B, we identified a total of five distinct subpopulations of keratinocytes, one T cell population, two subpopulations of mesenchymal cells (MSC), two subpopulations of fibroblasts, one subpopulation of myofibroblasts, one smooth muscle cell population (SMC), three subpopulations of vascular endothelial cells, one mast cell population, one population of lymphatic endothelial cells, one population of Schwann cells, and one population of antigen-presenting cells(APCs). Figure 1C demonstrates molecular markers characterizing distinct cellular subpopulations within psoriatic lesions.

We observed a significant increase in the number of vascular endothelial cells in the dermis of psoriasis patients (Figure 1D), which is consistent with previous research reports.[31,32] Among these, venous endothelial cells represent

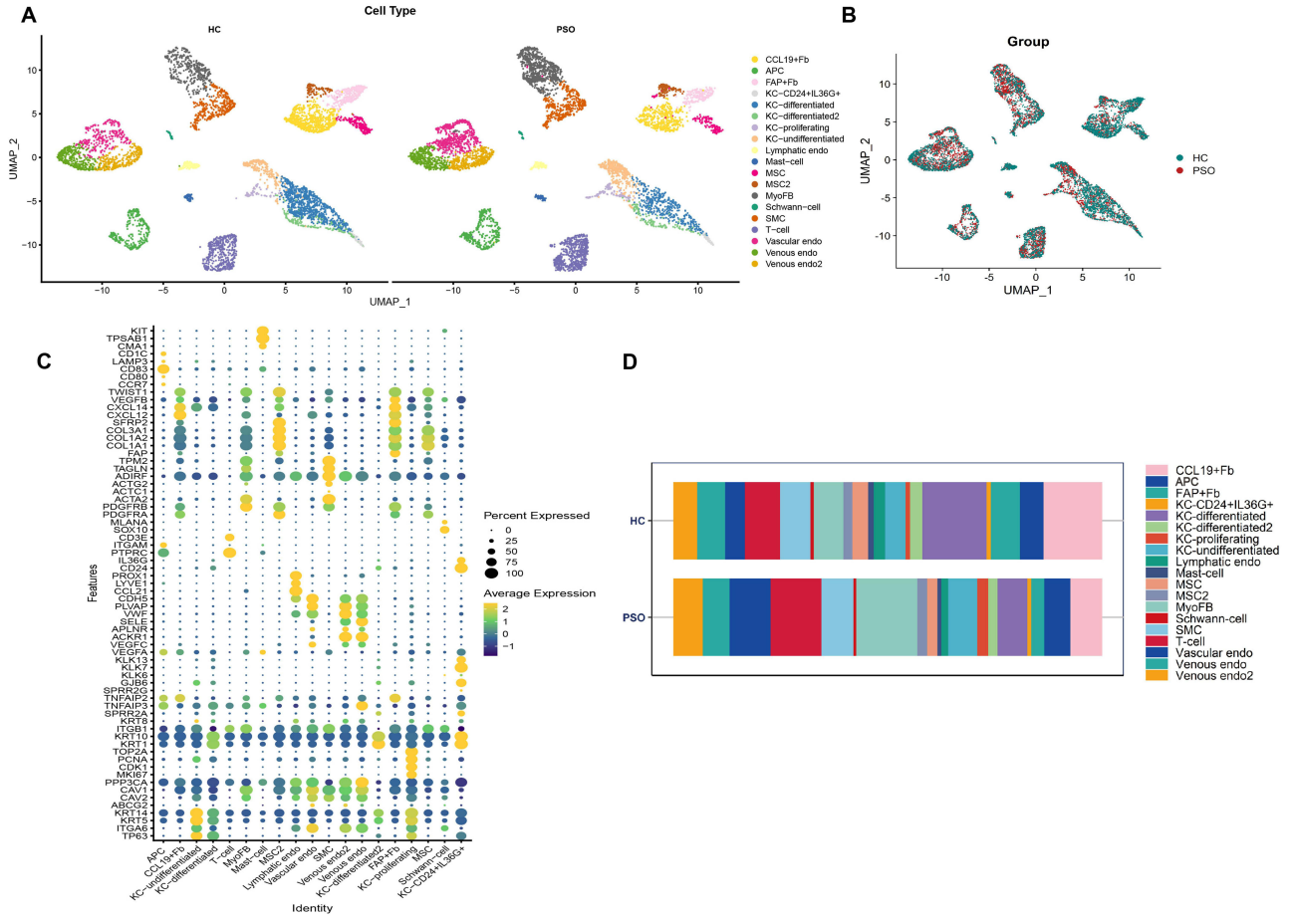

Figure 1 Integration analysis of scRNA-seq data from the psoriasis group and healthy control group. (**A**) UMAP dimensionality reduction plot showing the distribution of various cell populations after randomly selecting 5600 equal numbers of cells from the psoriasis group and healthy control group. (**B**) UMAP dimensionality reduction plot after integrating and clustering scRNA-seq data from three psoriasis patients and three healthy controls. (**C**) Dot plot illustrating the expression levels of selected marker genes for each cell type. (**D**) Bar graph displaying the composition ratios of different cell types in the psoriasis group and healthy control group.

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a crucial angiogenic subtype, with their characteristic retrograde migration forming nascent vessels exhibiting primitive vascular features.[33] We identified and characterized a novel subpopulation of microvenous endothelial cells, designated Venous endo2, which demonstrates: 1. Canonical venous endothelial markers (CD31/PECAM1, CD144/CDH5, VWF, ACKR1, CD105/ENG, NR2F2, CD93, S1PR1);[34] 2. High endothelial venule (HEV)-specific markers (IL33, ICAM1, TSPAN7, MEOX2, LIFR);[35–37] 3. Pro-inflammatory venous endothelial signatures (VCAM1, SELE, SELP, CCL14, IFITM3, CXCL12). Notably, Venous endo2 uniquely expresses IL-15, a key cytokine for tissue-resident memory T cell (TRM) development and maintenance. This finding gains particular significance given the emerging evidence supporting pathogenic TRM expansion as a critical driver of psoriatic pathogenesis.[38–41] Single - cell sequencing analysis shows that there are two functionally heterogeneous fibroblast subsets in the dermis of psoriasis. FAP+fibroblasts (Fibroblast activation protein - positive fibroblasts, FAP + Fbs) specifically overexpress fibroblast activation protein (FAP). This molecule is a classic marker of activated fibroblasts, common in cancer - associated fibroblasts (CAFs), but shows low expression or is silent in normal tissues.[42] Notably, besides the tumor microenvironment, FAP is also up - regulated in autoimmune diseases with pathological tissue remodeling, such as pulmonary fibrosis and rheumatoid arthritis.[43,44] The role of FAP in the development and progression of psoriasis remains to be studied. We found that FAP+ Fbs express molecules such as CXCL12, CXCL14, IL16, VEGFB, COL1A1, COL1A2, SFRP2, FBLN1, CTSK, ACKR3, CCN5, MMP2, and MMP27, which may play an important role in recruiting immune cells and remodeling the extracellular matrix in lesional skin. The other fibroblast subpopulation specifically expresses CCL19—a pivotal chemokine mediating naive T-cell and immature dendritic cell (DC) homing to lymphoid tissues.[45]

Transcriptional Characteristics and Functions of Vascular Endothelial Cell Subpopulations

As previously mentioned, we identified a novel subpopulation of microvenous endothelial cells, termed Venous endo2. Based on its gene expression characteristics, we suppose that it may play a significant role in the extravasation of immune cells, such as T cells, functioning similarly to high endothelial venules. To further investigate its characteristics, we performed differential gene analysis on Venous endo2 from the psoriasis group compared to Venous endo2 from the healthy control group using the FindAllMarkers function, followed by GO enrichment analysis of the upregulated differential genes. We found that the upregulated differential genes were enriched in biological processes such as vasculature development, blood vessel morphogenesis, tube development, blood vessel development, cell migration, tube morphogenesis, and angiogenesis. This suggests that Venous endo2 in psoriasis patients exhibits a high level of angiogenic activity compared to Venous endo2 in healthy controls, making it one of the key effector cells involved in the abnormal angiogenesis observed in the skin of psoriasis patients (Figure 2A). To further explore the transcriptional differences between vascular endothelial cell subpopulations in the skin of psoriasis patients and healthy controls, we employed SCENIC analysis, a method for transcription factor analysis using single-cell transcriptomic data. As shown in Figure 2B and Supplement Figure 1A (Details can be found in Tables S1 and S2 of the Supplementary Materials), we found that highly active transcription factors in Venous endo2 include PBX1, GRHL2, BCL11A, PLAG1, E2F1, MEOX1, and GATA4. Pre-B cell leukemia homeobox 1 (PBX1) expression is elevated in association with malignant phenotypes in cancer. In non-tumor environments, PBX1 has been shown to participate in the process of angiogenesis through its interaction with Hox factors.[46] There is substantial evidence indicating that PBX1 plays a role in maintaining proliferation signals, activating invasion and metastasis, and inducing angiogenesis in tumor tissues. The transcriptional target genes of PBX1 are associated with angiogenesis.[47,48] This suggests that PBX1 may be a key transcription factor inducing the functions of Venous endo2.

Identification of Infiltrating T Cell Subpopulations in Psoriatic Lesions of Psoriasis Patients

In recent years, attention has shifted to Th17 cells, as IL-17A and IL-17F secreted by Th17 cells lead to keratinocyte proliferation and the production of inflammatory factors, playing a central role in the pathogenesis of psoriasis.

To investigate the gene expression characteristics and heterogeneity of infiltrating T cells in psoriatic lesional skin, we reclassified the 1181 T cells obtained from scRNA-seq and performed differential gene analysis. Based on the

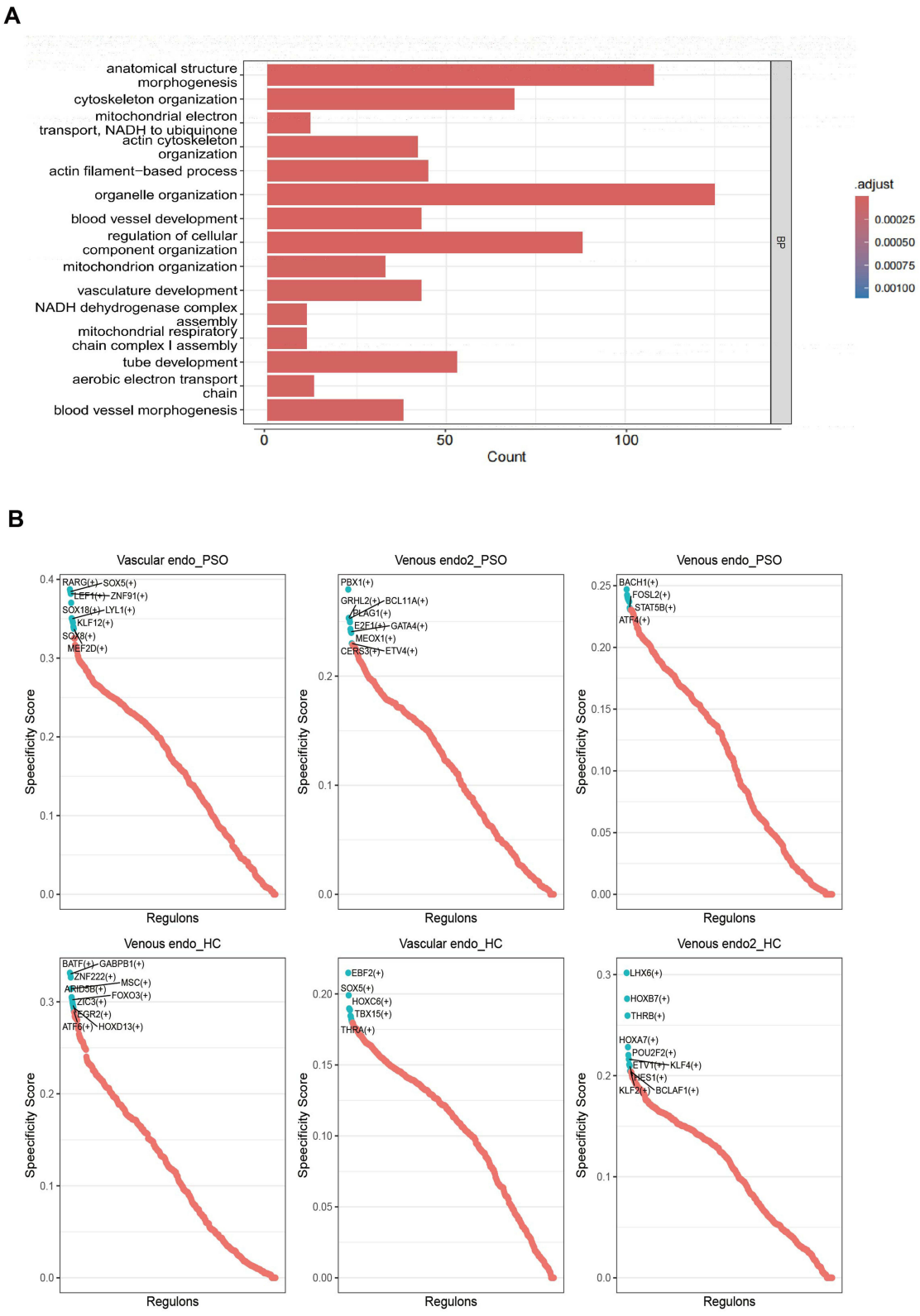

Figure 2 GO enrichment analysis and differential transcription factor molecules in vascular endothelial cells. (**A**) GO enrichment pathways of upregulated differential genes in Venous endo2 from the skin of psoriasis patients. (**B**) Active transcription factors in vascular endothelial cell subpopulations from the skin of psoriasis patients compared to those in healthy control skin.

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aforementioned differential gene analysis methods, these T cells were divided into six subpopulations (Figure 3A and B). This includes two CD8+ cytotoxic T cell subpopulations (CD8+ TC), which exhibit high expression of genes such as CD8A, IFNG, GZMA, GZMB, GZMK, GZMH, and NKG7, with some expression related to T cell exhaustion markers such as TIGIT, LAG3, and EOMES. There are also two effector memory T cell subpopulations (TEM), which show high expression of IL7R, COTL1, and LDHB, but do not express SELL. Additionally, we identified CD4-CD8- natural killer T cells (NKT), which display high expression of CD3E, NKG7, GNLY, and NCAM1 (Figure 3C–E). Most importantly, we identified a population of CD4+ tissue-resident memory T cell (CD4+TRM), which was found exclusively in the lesional skin of psoriasis patients and absent in the skin of healthy individuals (see Figure 3C red colored box). This population is characterized by high expression of genes such as IL17RA, IL22, PD1 (PDCD1), CXCR6, ITGAE, CD69, TNFRSF9, TNFRSF4, IL7R, CD4, and STAT3. We speculate that these cells play a crucial role in the onset and progression of psoriasis. Under normal conditions, the proliferation of TRM is regulated by negative feedback; however, this feedback balance is disrupted in disease states. TRM proliferate extensively in response to stimulus signals and release cytokines such as IL-17 and IL-22, further promoting TRM activation and exacerbating inflammation through positive feedback.

Identification of APC Cell Subpopulations

To analyze the pathogenic APC subpopulations in psoriatic lesions and to explore the transcriptional characteristics of APCs in the lesional skin, we performed subpopulation reclassification of the APCs obtained from scRNA-seq. As shown in Figure 4A–E, we identified a total of seven APC subpopulations, including one cDC1 subpopulation that specifically expresses XCR1 and CLEC9A. There are two cDC2 subpopulations, which specifically express CD1C. Notably, we found that the cDC2-1 subpopulation co-expresses the genes IL23A and IL1B, and exhibits high expression of the neutrophil chemokine CXCL8. These cytokines and chemokines are important pathogenic factors that initiate the onset of psoriasis. The main distinction between the cDC2-1 and cDC2-2 subpopulations is that cDC2-1, in addition to expressing inflammatory factors such as IL23A, also expresses the molecules CCR7 and CXCL16. CXCL16 can bind to CXCR6 on the surface of TRM cells, thereby promoting the stability and survival of TRM.[49] At the same time, we identified three subpopulations of perivascular macrophages (PVM).[8] These cells exhibit high expression of genes such as CD14, CD163, FOLR2, SELENOP, and RNASE1. In healthy control skin, the predominant subpopulation is PVM1, whereas in psoriasis patients, the main subpopulations are PVM2 and PVM3. Finally, we also identified a rare subpopulation of dendritic cells, termed mature DCs enriched in immunoregulatory molecules (mregDC).[50] As shown in Figure 4C and D, we found this cell population only in psoriasis patients, and it was not detected in healthy controls. This is consistent with the report by Satoshi Nakamizo,[51] this indicates that mregDCs are increased in number in psoriasis patients. As shown in Figure 4E, this cell population expresses high levels of the APC maturation molecules LAMP3 and BIRC3, and also exhibits high expression of the transcription factor IRF4. Additionally, they secrete large amounts of cytokines and chemokines, including IL-15, IL-32, CXCL16, CCL17, CCL19, and CCL22. The literature reports that mregDCs are a major source of IL-15 in psoriasis patients, and it is known that IL-15 is a factor that exacerbates inflammation in psoriasis.[52,53]

Cell2location Combined with MISTy Analysis Reveals the Co-Localization Relationships of Celltypes

Due to the technical limitations of spatial transcriptomics with 10x Visium, each spot contains several to dozens of cells. We improved the resolution by assessing the cellular composition within each spot. Using previously classified scRNA-seq data as a reference, we performed deconvolution for each spot to obtain the spatial distribution density of each cell type. Based on the deconvolution results (Figure 5A), we observed potential co-localization relationships among FAP +Fbs, T cells, Venous endo2, and APCs in psoriasis patients. Next, we tested whether the distribution density of major cell types within each spot could be predicted by the spatial context formed by the composition of neighboring cell types, specifically the co-localization relationships we observed. We utilized MISTy to assess the cellular distribution relationships of each spot in the spatial transcriptomics data with its 15 adjacent spots. As shown in Figure 5B, we observed

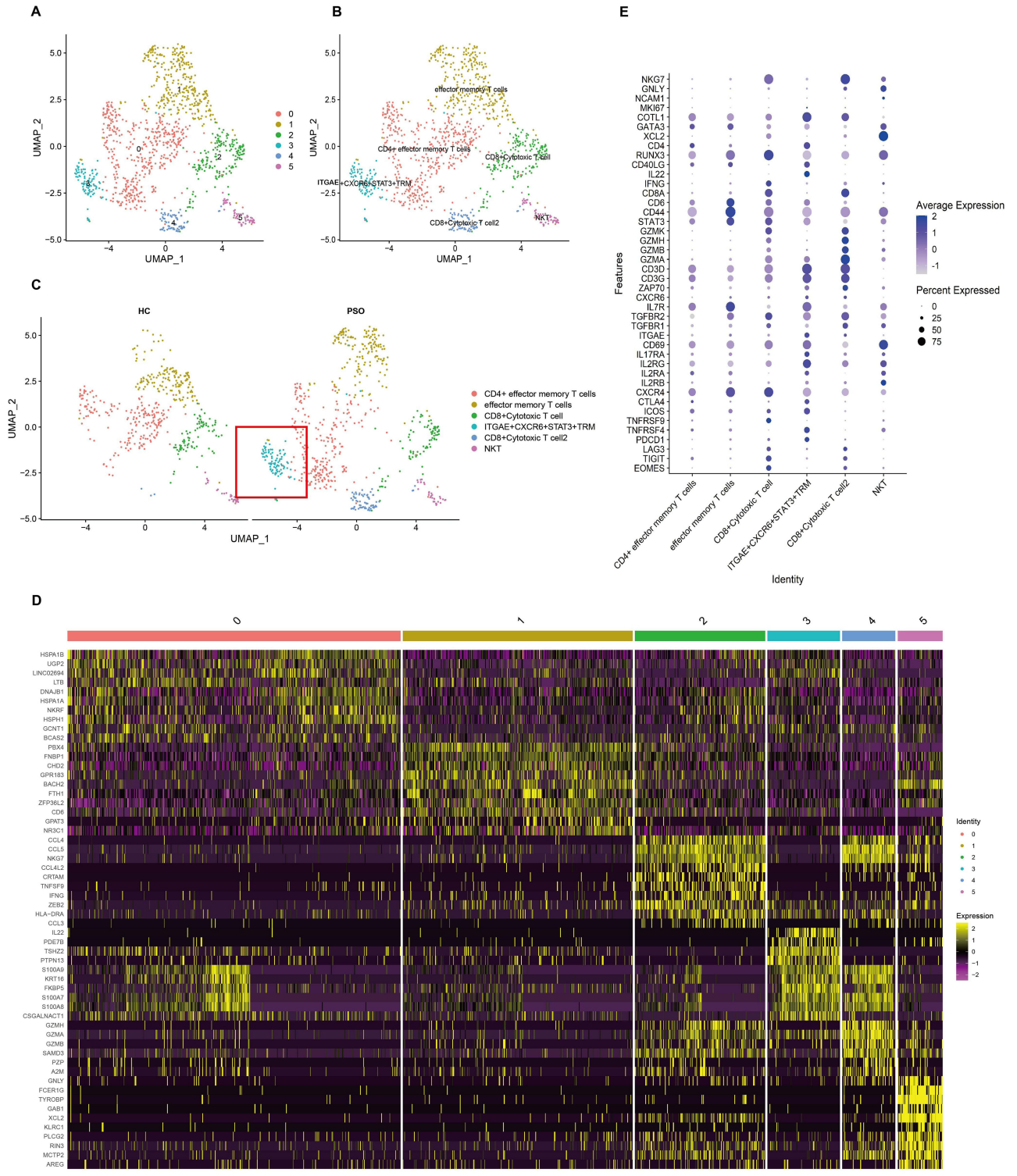

Figure 3 scRNA-seq defines T cell subpopulations in the psoriasis group and healthy control group. (**A** and **B**) After reclassifying T cells in the psoriasis group and healthy control group into subpopulations, UMAP visualization was used to present a total of six distinct T cell subpopulations. (**C**) The T cell subpopulations identified in the psoriasis group and healthy control group are presented separately in UMAP plot format. ITGAE+CXCR6+STAT3+ TRM cells were identified in the lesional skin of psoriasis patients, whereas they were absent in the healthy controls (see red colored box). (**D**) The heatmap displays the top 10 differential genes for six distinct T cell subpopulations. (**E**) the expression levels of marker genes in different T cell subpopulations in dot plot format.

a significant co-localization among FAP+ Fbs, T cells, APCs, and Venous endo2. This co-localization was notably enhanced in the psoriatic lesions of psoriasis patients (see red colored box), while it was absent in the healthy control skin. This suggests that the spatial niche formed by these four cell types may represent an important pathogenic niche in

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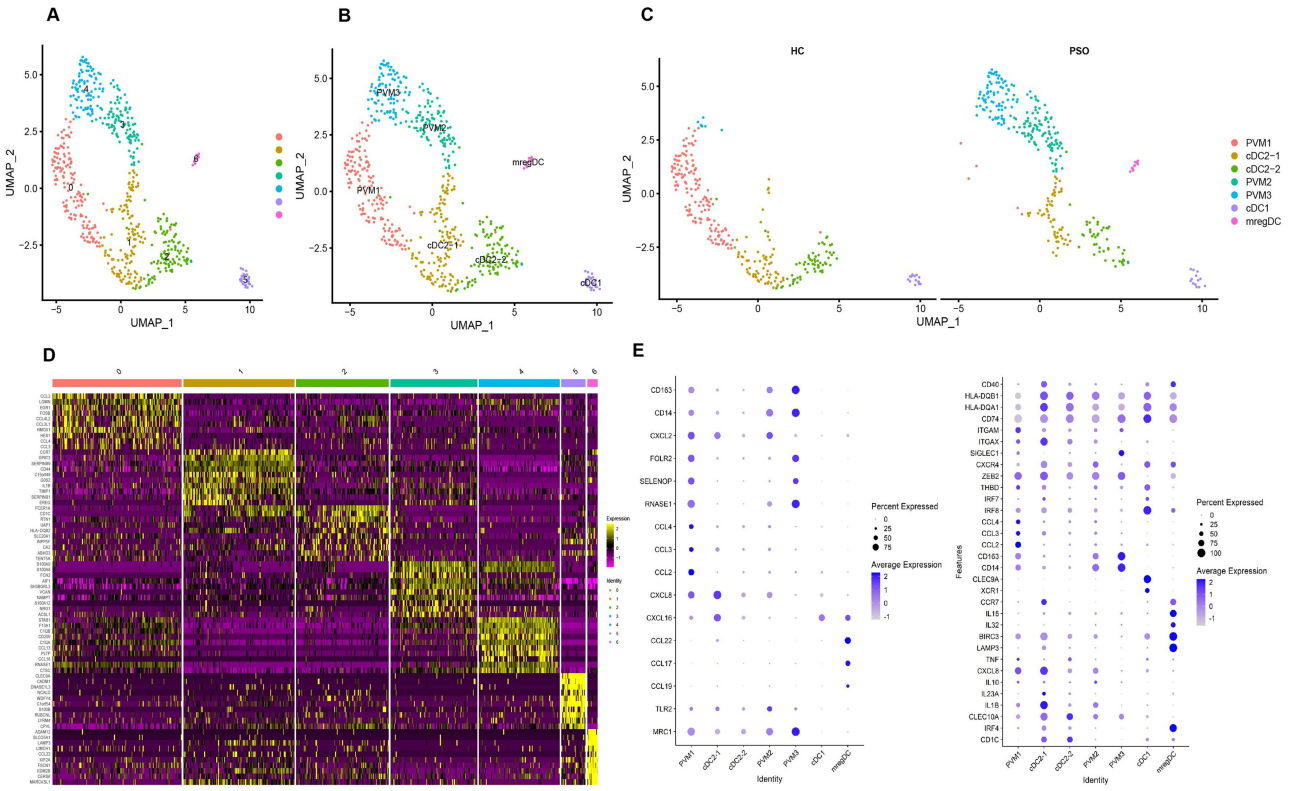

Figure 4 scRNA-seq defines APC subpopulations in the psoriasis group and healthy controls. (**A** and **B**) After reclassifying APCs in the psoriasis group and healthy control group into subpopulations, UMAP visualization was used to present a total of seven distinct APC subpopulations. (**C**) The APC subpopulations identified in the psoriasis group and healthy control group are presented separately in UMAP plot format. (**D**) The heatmap shows the top 10 differential genes for seven distinct APC subpopulations. (**E**) The expression levels of marker genes in different APC subpopulations are presented in dot plot format.

the lesions of psoriasis patients. Subepidermally and above the dermal papillae is the primary site of pathogenic T cell infiltration in psoriatic skin lesions. Previous studies have noted that a large number of T cells are in close contact with antigen-presenting cells in this location, which may lead to the activation of naïve T cells.[54] To further validate the above results and explore the relationship between Venous endo2 and FAP+ Fbs, T cells, APCs. We conducted GSVA analysis to investigate the enrichment of their differential genes and the correlation of differential gene enrichment scores in the RNA-seq dataset GSE121212. GSE121212 includes RNA-seq data from 28 patients with plaque psoriasis and 38 healthy controls. As shown in Figure 5C, the results indicate that the enrichment scores of differential genes for Venous endo2 in the skin are significantly correlated with the enrichment scores of differential genes for T cells and APCs ($P < 0.05$). However, the correlation with the enrichment scores of differential genes for FAP+ Fbs is relatively weak and not significant ($P > 0.05$). These findings further validate the co-localization relationships among Venous endo2, FAP+Fbs, T cells, and APCs.

Spatial Distribution of Pathogenic Signaling Pathways in the Skin of Psoriasis Patients

Abnormal signaling pathways can lead to autoimmune diseases. Inflammatory cytokines such as TNF-α, IL-17, IL-23, IL-22, and VEGF create a complex inflammatory signaling network in psoriatic skin lesions. Dysregulated signaling pathways can drive the development of autoimmune diseases. Conventional gene expression-based methods for inferring pathway activity suffer from two fundamental limitations: 1. Failure to account for differential gene-level contributions to pathway activity. 2. Inability to incorporate post translational modifications and downstream regulatory effects, leading to distorted activity assessments. By leveraging large-scale publicly available perturbation experiments, PROGENy generates core gene sets for specific signaling pathways, thereby addressing these constraints. For each gene, using pathway perturbation as the independent variable and Z - score as the dependent variable, it builds a linear regression model to

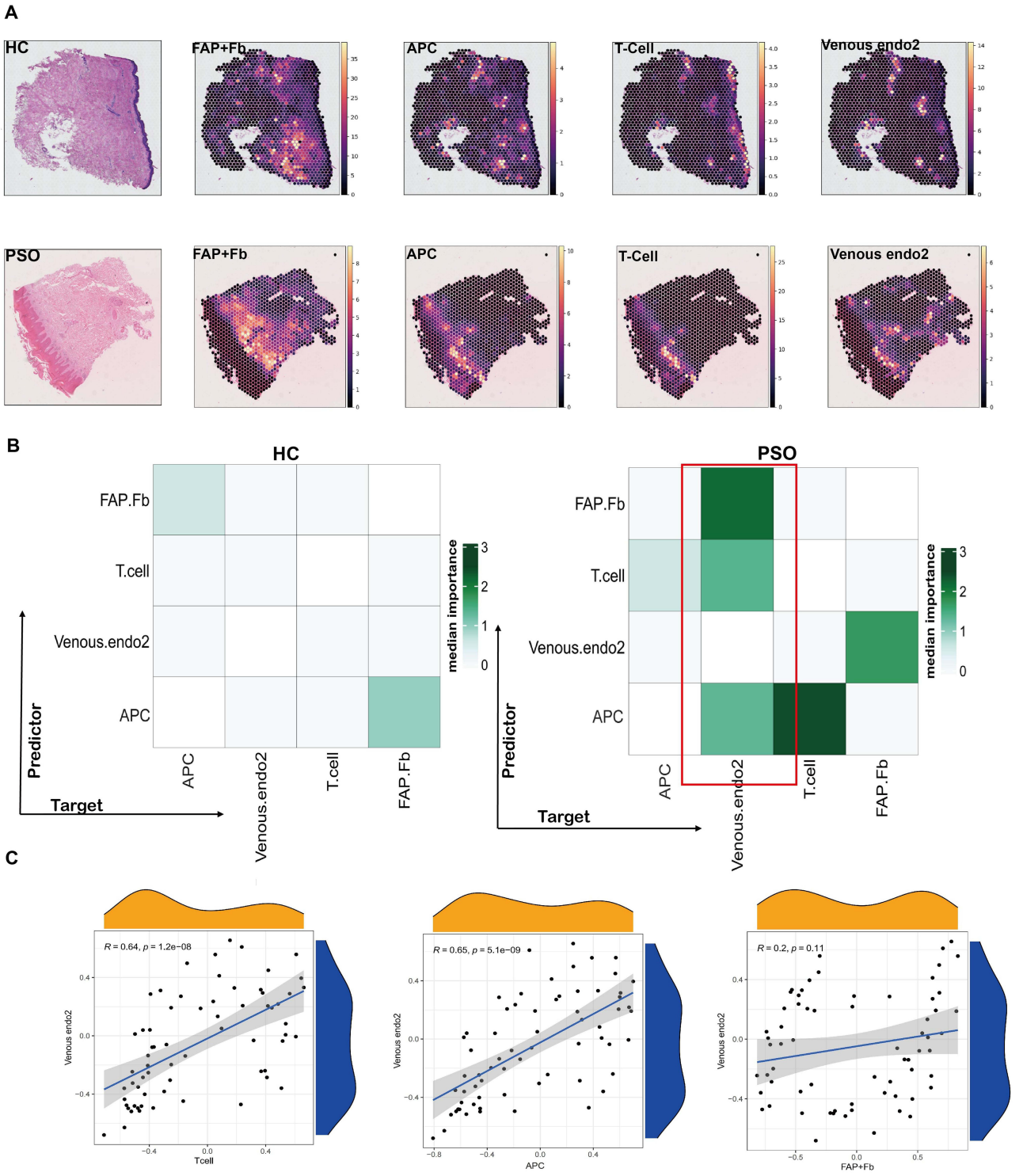

Figure 5 Spatial co-localization of cell type distributions. (**A**) After training the cell type reference matrix using Cell2location on the scRNA-seq dataset of psoriasis skin, we performed deconvolution to display the spatial distribution density of each cell type on the spatial transcriptomics data. (**B**) In the spatial transcriptomics data of psoriasis patients and healthy controls, MISTy was used to detect the co-localization relationship between the distribution of a specific cell type at each point and the distribution of other cell types in the surrounding 15 points. A higher importance value indicates a stronger co-localization relationship. In psoriatic skin lesions, Venous endo2, FAP+Fbs, T cells, and APCs demonstrate spatial co-localization, as indicated by red box. (**C**) Using the RNA-seq dataset GSE121212, we performed GSVA scoring for the gene sets of each cell type. Subsequently, we conducted a correlation analysis between the enrichment scores of Venous endo2 and the enrichment scores of the other cell types.

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identify the Top 100 genes with the largest contribution to the pathway. It then forms the PROGENy core gene set using Z - coefficients as weight values. Unlike simple pathway mapping methods, PROGENy can accurately infer signaling pathway activity from gene expression in different states. Urbation experiments to identify core pathway-specific gene sets.[25,55] Based on the gene expression data from spatial transcriptomics, the PROGENy algorithm can calculate the activity score for each pathway at each spot, allowing us to identify regions with high and low cellular pathway activity. This provides insights into the spatial characteristics of abnormal signaling pathway distribution in disease states. As shown in Figure 6A, we observed a significant increase in the activity of the JAK-STAT pathway, VEGF pathway, and TNF-α pathway in the lesions of psoriasis patients. TNF-α inhibitors have already been successfully applied in clinical settings.[56] Some JAK inhibitors, such as TYK2 inhibitors, have also garnered substantial clinical evidence.[57,58] In case reports, the use of VEGF inhibitors in patients with certain cancers accompanied by psoriasis has also resulted in the improvement of skin lesions.[59] To link tissue structure with tissue function, we analyzed the spatial dependence between signaling pathways and cell types. We used MISTy to assess the co-localization relationship between cellular distribution density and pathway activity scores at each point in the spatial transcriptomics data. As shown in Figure 6B, compared to healthy control skin, there is a significant co-localization relationship between the activity of the NF-κB pathway, the TNF-α signaling pathway, and keratinocytes in the lesions of psoriasis patients (Figure 6B). The NF-κB and TNF-α signaling pathways are key pathways for activating keratinocytes, and targeting the NF-κB signaling pathway may represent a promising therapeutic approach for psoriasis.[60] TGF-β signaling and JAK-STAT signaling are critical for the survival of immune cells. We found that the co-localization of these two signals with APC and T cells is enhanced in the disease state (Figure 6B).

Multi-Channel Immunofluorescence Provided Spatial Validation of the Disease-Associated Pathological Niche Originally Revealed by Combined Spatial Transcriptomic and scRNA-Seq Analyses

Multiplex immunofluorescence in Figure 7A demonstrates fibroblast co-localization with T cells, antigen-presenting cells, and venous endothelial cells in psoriatic lesions. In the skin of healthy controls, however, the colocalization structures were not detected, as can be seen in Supplement Figure 1B. Figure 7B provides a schematic representation of these spatial interactions.

Discussion

This study integrates scRNA-seq, spatial transcriptomics, and bulk RNA-seq data to investigate the co-localization patterns and transcriptional characteristics of immune cells and stromal cells in the skin of psoriasis patients.

TLS, also known as tertiary lymphoid organs or ectopic lymphoid tissues, form in non-lymphoid organs during chronic inflammation (including cancer, infections, and autoimmune diseases). While TLS involved in cutaneous immunity remain poorly defined, a similar structure termed " inductive skin-associated lymphoid tissue (iSALT)" has recently been proposed. Identified in mice, iSALT transiently emerges around post-capillary venules in response to immunogenic stimuli (eg, haptens or infections). And comprises leukocytes including perivascular macrophages, DCs, and T cells. iSALT-like perivascular leukocyte infiltrates are frequently observed in inflammatory skin diseases, but these may merely reflect leukocyte extravasation, and whether effector T cell activation occurs within these structures is unknown. Notably, such iSALT-like structures are prominently observed in psoriasis histopathology (H&E staining), though their cellular composition and functional roles remain elusive. By integrating multi-omics data (including spatial transcriptomics), we comprehensively characterized the co-localization patterns and transcriptional profiles of immune/stromal cells in psoriasis skin. High-quality scRNA-seq data revealed a unique microvascular endothelial subset—Venous endo2—expressing both post-capillary venule markers and TLS-associated HEV signatures, suggesting its potential role in iSALT-like structure formation. To map Venous endo2 spatially and analyze its cellular interactions, we performed Cell2location-based deconvolution of scRNA-seq derived cell types onto spatial transcriptomics data, generating spatially resolved cell density maps. Co-localization analysis demonstrated significant spatial associations between Venous endo2 and T cells, APCs, and FAP+Fbs. Combined with histopathological evidence, we propose these clusters represent iSALT-like structures in psoriasis.

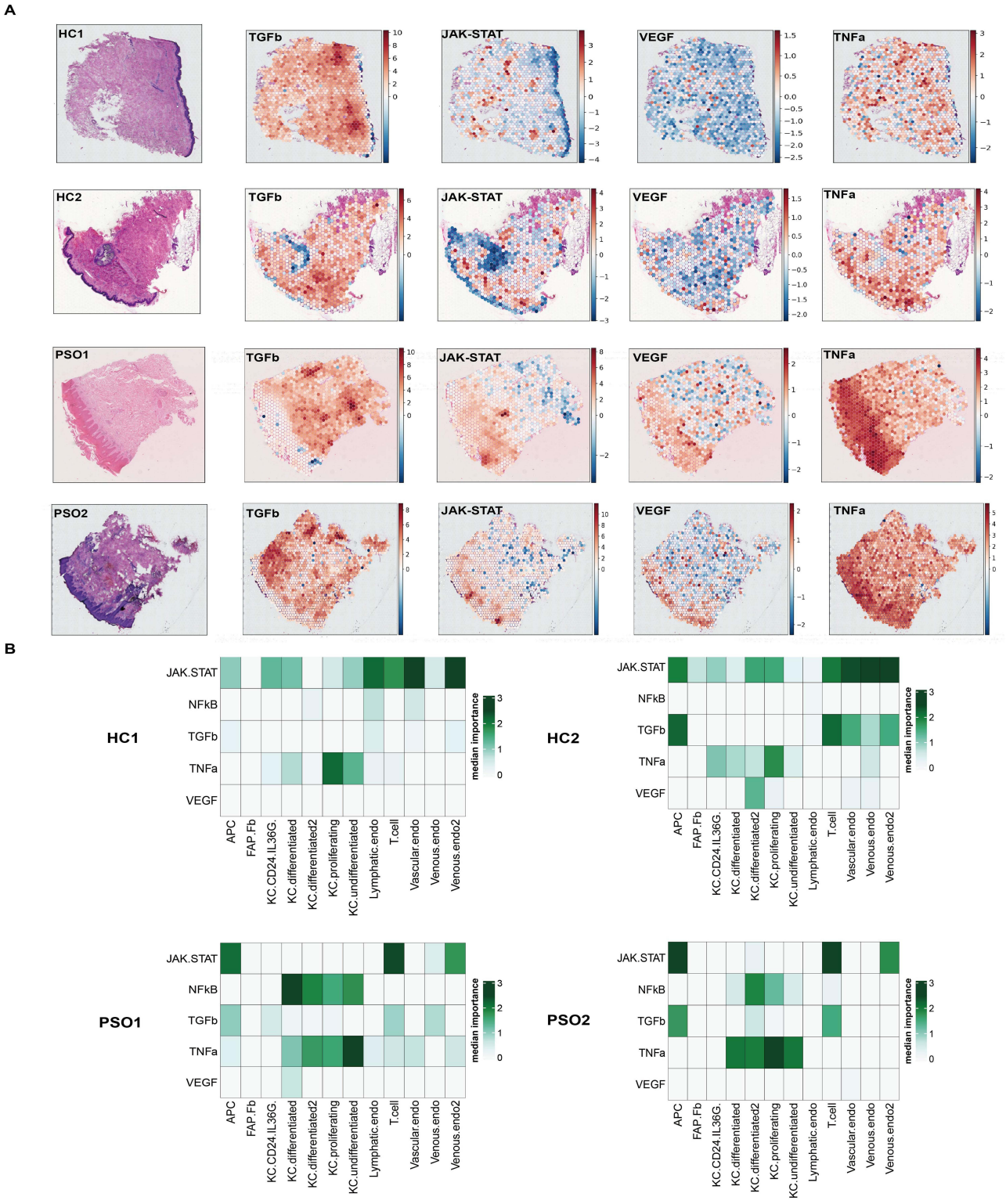

Figure 6 Differences in signaling pathway activity in the spatial transcriptomics of psoriasis patients versus healthy controls, and the co-localization relationships between cell types and signaling pathways. (**A**) Activity of TGF-β, JAK-STAT, VEGF, and TNF-α, signaling pathways at each point in the spatial transcriptomics of psoriasis patients versus healthy controls. (**B**) The co-localization relationship between the activity of different signaling pathways and the distribution density of various cell types at each point in the spatial transcriptomics of psoriasis patients versus healthy controls. A higher Importance value indicates a stronger co-localization relationship.

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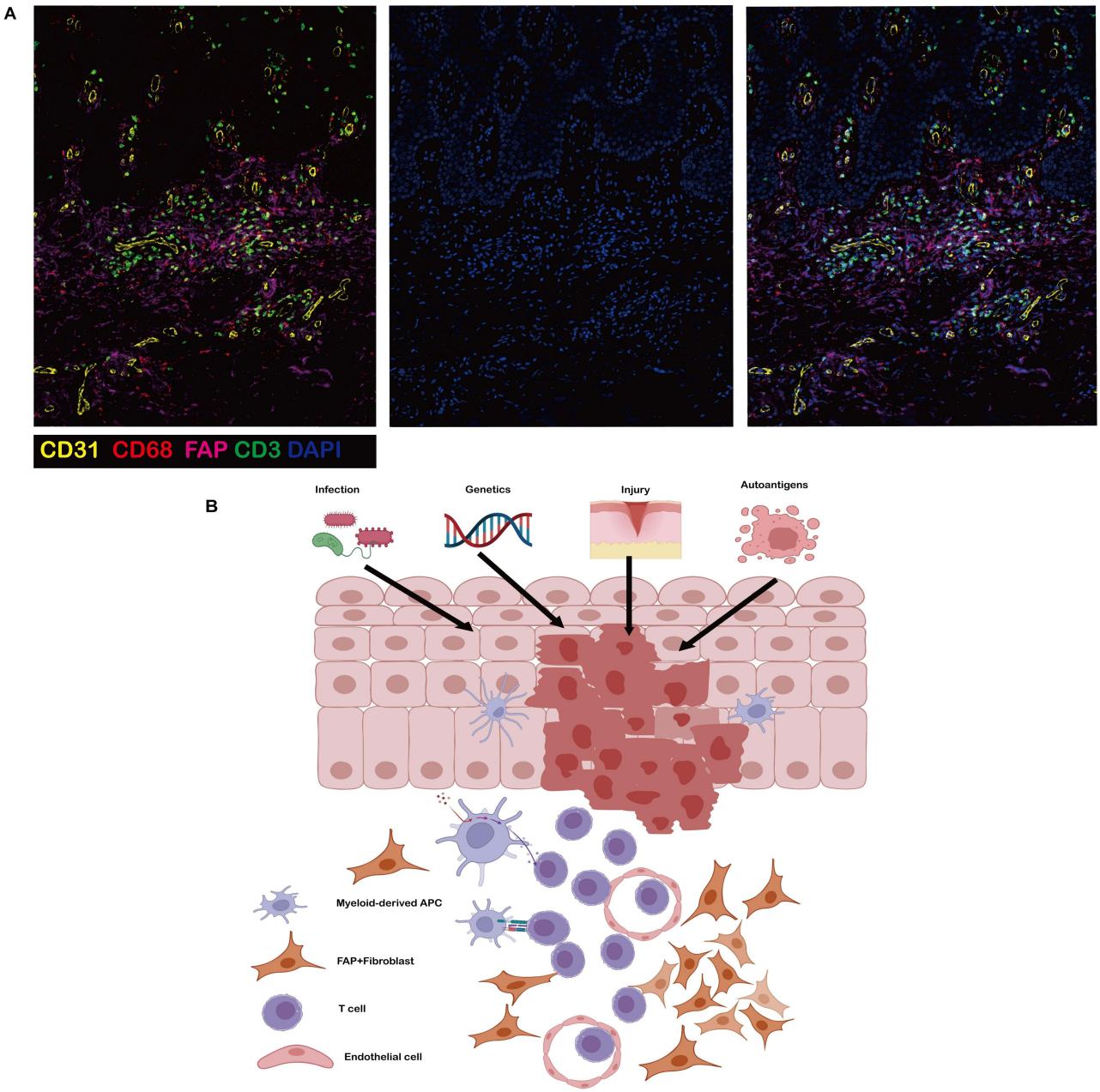

Figure 7 Multiplex immunofluorescence delineates the pathological niche within psoriatic skin lesions. (**A**) Multiplex immunofluorescence spatially resolves the co-localization of microvascular endothelia (CD31), T cells (CD3), fibroblasts (FAP), and myeloid-derived antigen-presenting cells (CD68) within psoriatic niches. (**B**) Psoriasis may be triggered by various factors, including skin injury (Koebner phenomenon) in genetically susceptible individuals, infections, medications, and autoantigens. These predisposing factors ultimately lead to the activation of antigen-presenting cells (APCs), recruiting T cells and activating fibroblasts. These cells cooperatively form a potential pathological niche with endothelial cells locally, which exacerbates tissue damage.

An imbalance of Th17 and Treg cells has been observed in the lesional skin and peripheral blood of patients with moderate to severe plaque psoriasis. Compared to healthy controls, the expression of TRM (tissue-resident memory T cell) marker genes (CD103, CD69, CD49, CXCR6) is elevated in the lesional skin of psoriasis patients. After systemic treatment with methotrexate, IL-17 monoclonal antibodies, or TNF-α monoclonal antibodies, assessments revealed a significant reduction in the expression of TRM-related markers.[38] However, these memory T cells can still be found in areas of lesion regression, and under certain conditions, they can rapidly respond to cytokines secreted by cells such as DC and become reactivated, leading to a recurrence of psoriasis.[61,62] TRM can be classified into TRM1 and TRM17; the former is functionally similar to Th1 cells, while the latter is functionally similar to Th17 cells.[63] Infection is a significant factor leading to the generation of

TRM cells.[64] Researchers have identified CD4+ TRM cells with Th17 characteristics in the kidneys of patients with neutrophil cytoplasmic antibody-associated glomerulonephritis. Experimental animal models have demonstrated that renal TRM17 cells are induced by pathogenic microorganisms infecting the kidneys, such as Staphylococcus aureus, Candida albicans, and uropathogenic Escherichia coli, and they persist in the kidneys even after these infections are controlled. Following the induction of experimental glomerulonephritis, these renal TRM17 cells exacerbate renal pathological damage by producing IL17A upon stimulation.[65] The above studies suggest that TRM may play an important role in the pathogenesis and recurrence of psoriasis. Specifically, the body is unable to maintain a balance between anti-infection and autoimmunity, and the abnormal proliferation of TRM exacerbates the local inflammatory response.

Concurrently, our analysis identified a novel CD4+ TRM subset that is exclusively present in lesional skin of psoriasis patients but absent in healthy skin. This population exhibits characteristic markers including IL17RA, IL22, PD1 (PDCD1), CXCR6, ITGAE, CD69, TNFRSF9, TNFRSF4, IL7R, CD4, and STAT3. Notably, these cells robustly express IL-22, a pivotal pathogenic cytokine in psoriasis. IL-22 enhances the anti-apoptotic capacity of keratinocytes, thereby driving their hyperproliferation and aberrant differentiation, IL-22 also induces STAT3 phosphorylation and mediates the expression of inflammation-associated genes.[66] Therefore, this T-cell subset may represent a critical pathogenic T-cell population in psoriasis patients. It holds promise as both a biomarker for assessing disease activity/severity and a novel therapeutic target. Further investigation into the biological properties and functional mechanisms of this subset will advance our understanding of psoriasis pathogenesis. The cytokines that induce TRM formation include TGF-β, IL-33, and TNF-α. These cytokines downregulate the expression of the T-cell transcription factor Kruppel-like factor 2 (KLF2) and its target genes, thereby promoting the retention of CD8+ T cells in skin tissues.[67] Cytokines supporting TRM maintenance and homeostasis, such as IL-15, IL-12, IL-7, and IL-18, play critical roles in TRM development.[68] Our analysis revealed a particularly intriguing finding: beyond dendritic cells (DCs), which secrete TRM-inducing and sustaining cytokines, post-capillary venular endothelial cells also produce IL-33 and IL-15. This suggests that endothelial cells in psoriatic skin may not only mediate inflammatory cell extravasation but also contribute to TRM maturation and survival.

Subsequently, we used PROGENy to investigate the activity of different signaling pathways in the spatial transcriptomics data of psoriasis patients compared to healthy controls, as well as the colocalization of these pathways with cell types. We found that the activity of the TNF-α signaling pathway, JAK-STAT signaling, and VEGF signaling was significantly enhanced in psoriasis patients, while there were no notable changes in TGF-β signaling. Through co-localization analysis of signaling pathways and cell types, we discovered that in psoriatic lesions, there is a significant co-localization relationship between TNF-α and NF-κB signaling with pathological keratinocytes. NF-κB is one of the downstream signals of TNF-α, and it can mediate immune and inflammatory pathways, cell proliferation and differentiation, as well as apoptosis.[69] Genome-wide association studies have linked psoriasis with several signaling mediators in the NF-κB pathway. Genetic variations in IL-23 and the NF-κB pathway together can lead to severe psoriasis.[70,71] Compounds that specifically target NF-κB signaling may serve as a new therapy for treating psoriasis.[72] In the future, utilizing advanced spatial transcriptomics sequencing technologies will enable more precise quantitative analyses of these pathogenic signals. This will aid in optimizing drug selection and evaluating treatment efficacy for different psoriasis patients.

Our study has several limitations. First, the pathological niche we identified in psoriasis patients (co-localization of Venous endo2 with T cells, APCs, and FAP+ Fbs) was not validated in a large cohort of patients. This includes determining whether this structure correlates with disease activity in psoriasis patients and whether effective treatment reduces its presence. Additionally, the study did not include post-treatment samples. These aspects represent important directions for our future research. Second, our conclusions are primarily based on bioinformatic analysis and lack experimental validation. Furthermore, our single-cell sequencing data were derived from full-thickness skin samples, while the spatial transcriptomics samples came from the dermis. These are significant shortcomings of our study. Finally, the sequencing sample size included in our research was too small, limiting the persuasiveness of our conclusions. In autoimmune diseases, the formation of tertiary lymphoid structures serves as a diagnostic criterion and a marker of disease activity. Given the similarity of the pathological niche we identified, we believe it could potentially be an important indicator for assessing disease activity in psoriasis. Lastly, we propose a vision: The application of spatial transcriptomics and single-cell sequencing holds great promise for personalized treatment and treatment efficacy evaluation in psoriasis patients. The wider adoption and application of these technologies will benefit many more patients.

Table 1 Encompassing All Types of Omics Datasets Included in Our Study

GEO Accession	Disease Type	Samples	Technology
GSE121212	Plaque-type psoriasis	Skin tissue	RNA sequencing
GSE225475	Plaque-type psoriasis	Skin tissue	Spatial transcriptomics
GSE162183	Plaque-type psoriasis	Skin tissue	scRNA-seq

Conclusion

We identified a potential pathogenic niche in psoriasis patients, composed of Venous endo2, FAP+ Fbs, T cells, APCs. This distinct pathogenic niche may serve as a platform that sustains activated immune cells, thereby exacerbating psoriatic skin pathology.

Data Sharing Statement

All data are available for download from the GEO database, as detailed in Table 1.

Ethics Statement

All data in this study were sourced from publicly available databases. Each participant received ethical approval and informed consent for the respective study, as detailed in the original publication. Skin lesion specimens from psoriasis patients were obtained from Jinling Hospital, Affiliated Hospital of Nanjing Medical University. All participants provided written informed consent, and the study protocol was approved by the Ethics Committee of Jinling Hospital, Nanjing Medical University. All studies involving human participants were conducted in accordance with the ethical principles of the Declaration of Helsinki.

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Disclosure

The authors report no conflicts of interest in this work.

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