

Single-Cell Transcriptomics Reveals RNA-Binding Protein-Associated Cellular Heterogeneity and Regulatory Networks in Psoriatic Skin

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Background: T cell differentiation, aberrant keratinocyte proliferation, and immune cell infiltration are the hallmarks of psoriasis, a chronic inflammatory skin condition. The expression patterns of RNA-binding proteins (RBPs), which are important post-transcriptional regulators of gene expression, in psoriatic skin remain largely unexplored. Dysregulation of RBPs has been implicated in the pathogenesis of various illnesses.

Methods: In order to describe cellular composition, RBP expression heterogeneity, and intercellular communication networks, we methodically examined single-cell RNA sequencing (RNA-seq) data in this work. To identify RBP expression subgroups across various cell types, such as keratinocytes, dendritic cells, and T cells, 2141 known RBP genes were utilized for unsupervised clustering. RBP-associated functional pathways were found using Gene Ontology (GO) enrichment and co-expression network analysis. Cell-to-cell communication was examined using CellChat analysis. Additionally, RBP-associated alternative splicing events in psoriasis were assessed by integrating bulk RNA-seq data.

Results: When compared to healthy skin, psoriatic skin showed higher percentages of T cells and dendritic cells and lower percentages of keratinocytes. Different disease-associated RBP expression subgroups were identified by RBP-based clustering, particularly in keratinocytes, dendritic cells, and T cells. Differentially expressed RBPs were shown to be primarily involved in keratinocyte differentiation, immunological responses, antigen processing and presentation, inflammation, and apoptosis, according to functional studies. Significantly increased interactions between keratinocytes and immune cells in psoriasis were revealed by cell-cell communication analysis. These interactions involved important signaling pathways like major histocompatibility complex (MHC)-I/II, macrophage migration inhibitory factor (MIF), C-C motif chemokine ligand (CCL), and cluster of differentiation 99 (CD99). Additionally, integration with bulk RNA-seq data showed extensive alternative splicing changes in psoriatic skin, which were closely associated with dysregulated RBP expression.

Conclusion: Through controlling keratinocyte function and immune cell activation, RBPs may contribute to the etiology of psoriasis. This study offers a comprehensive characterization of RBP expression across several cell types in psoriatic skin.

Keywords: psoriasis; RNA-binding proteins; single-cell RNA sequencing; keratinocytes; immune cells; heterogeneity

Introduction

About 2–3% of people worldwide suffer from psoriasis, a chronic inflammatory skin condition caused by the immune system [1]. It is characterized by repeated erythematous plaques, excessive keratinocyte (KC) growth, and dysregulated immunological responses, significantly lowering patients' quality of life. The exact pathophysiology of psoriasis remains unclear, although genetic susceptibility, environmental triggers, infection, metabolic disruption, and psychological stress are known to contribute [2,3]. A growing body of research indicates that abnormal interactions between immune cells and KCs play a key role in the devel-

opment and maintenance of illness. T cells have traditionally been thought to be the main causes of psoriatic inflammation. Cytokines like interferon- γ (IFN- γ), tumor necrosis factor- α (TNF- α), interleukin-17 (IL)-17, and IL-22 are produced by activated Cluster of Differentiation (CD) 4+ T cell subsets, such as Th1 and Th17 cells, which support inflammatory cascades and encourage KC hyperproliferation [4,5,6]. By secreting proinflammatory cytokines and promoting Th1-like responses, CD8+ T cells also contribute to disease progression. Within psoriatic lesions, innate and accessory immune cells, such as neutrophils, macrophages, and dendritic cells (DCs), simultaneously create a complex

inflammatory network [7,8]. Chronic inflammation is reinforced by DC-derived cytokines that promote T cell activation and polarization, including IL-23, IL-12, and type I interferons. Furthermore, KCs are now regarded as active actors in the pathophysiology of psoriasis rather than passive targets. They can produce alarmins, cytokines, and antimicrobial peptides that activate plasmacytoid DCs and amplify immunological responses, thereby creating a self-sustaining inflammatory cycle [9,10]. These results emphasize the significance of intercellular communication and cellular heterogeneity in psoriasis.

By forming ribonucleoprotein complexes, RNA-binding proteins (RBPs) regulate RNA splicing, stability, localization, and translation, making them key regulators of posttranscriptional gene expression [11]. RBPs are crucial for preserving cellular identity and homeostasis because they regulate the fate of hundreds of RNA targets. RBP dysregulation has been linked to various human diseases, such as inflammatory conditions and cancer [12,13]. Crucially, cell type-specific RBPs shape cell-specific functional phenotypes by controlling important processes including translational regulation and alternative splicing [14,15]. However, the expression landscape and regulatory roles of RBPs across distinct skin cell populations during psoriasis remain largely unexplored.

A potent method for analyzing cellular heterogeneity and transcriptional dynamics at single-cell resolution is single-cell RNA sequencing (scRNA-seq) [16]. This method has been widely used in inflammatory skin disorders to identify previously unknown cellular subpopulations, map immune and stromal cell diversity, and characterise intercellular networks [17]. Significant variability among KCs, T cells, and DCs, as well as modified cytokine-driven communication networks among cell types, have been identified by recent scRNA-seq studies in psoriasis [18,19,20]. Nevertheless, the majority of research has been on transcriptional control and cytokine signaling, whereas posttranscriptional regulatory mechanisms—particularly RBP-mediated networks—remain poorly understood.

In order to thoroughly investigate the cellular heterogeneity and RBP-candidate association networks in psoriatic skin, we combined single-cell and bulk transcriptome data. We further explored intercellular communication and alternative splicing alterations to elucidate the potential posttranscriptional mechanisms underlying immune-epithelial crosstalk in psoriasis. Our findings provide new insights into RBP-mediated regulation in skin inflammation and may offer potential targets for therapeutic intervention.

Methods

Data Acquisition and Preprocessing

The scRNA-seq data of human skin samples were obtained from the Gene Expression Omnibus (GEO, <http://www.ncbi.nlm.nih.gov/geo/>) database under accession

number GSE151177. The dataset included skin tissues from healthy controls (n = 5) and psoriasis patients (n = 13). Since the number of cells selected from the sample Control_5 was too small, only around 50 cells were obtained, we thus excluded the sample Control_5. Thus, we selected healthy controls (n = 4) and psoriasis patients (n = 13) for analysis. Raw scRNA-seq data were processed using the Seurat package (version 4.3.0, <https://satijalab.org/seurat/>) in R (version 4.3.1, <https://www.r-project.org/>). Cells with low transcript counts, excessive mitochondrial gene expression, or low gene detection rates were excluded to ensure high-quality downstream analyses. Specifically, cells expressing fewer than 200 genes, more than 6000 genes, or containing >10% mitochondrial transcripts were removed. Genes detected in fewer than three cells were also excluded.

Bulk RNA sequencing (RNA-seq) data from healthy skin tissues and psoriatic lesions were downloaded from the Sequence Read Archive (SRA, <https://www.ncbi.nlm.nih.gov/bioproject/>) database under accession number PRJNA481993. The raw reads were trimmed of low-quality bases using a FASTX-Toolkit (version 0.0.13; http://hann.onlab.cshl.edu/fastx_toolkit/) was used to trim the data by removing low-quality bases (Remove the base with terminal mass less than 20; Remove 30% of the reads whose base mass is less than 20) in raw reads. Subsequently, the clean reads were evaluated using FastQC (<http://www.bioinformatics.babraham.ac.uk/projects/fastqc>). Clean reads were then aligned to the human reference genome GRCh38 (GRCh38.p13, Gencode v38, downloaded on June 7, 2021 from https://www.gencodegenes.org/human/release_38.html) using HISAT2 (version 2.2.1, <https://daehwan.kimlab.github.io/hisat2/>) [21]. Uniquely mapped reads were screened for further analysis. We then calculated the reads number located on each gene. The expression levels of genes were evaluated using FPKM (fragments per kilobase of exon per million fragments mapped). DESeq2 (version 1.38.3, <https://bioconductor.org/packages/DESeq2/>) software [22] was used to perform differential gene expression analysis using the reads count file. DESeq2 was also used to analyze the differential expression between two or more samples and thus determine whether a gene was differentially expressed by calculating the fold change (FC) and false discovery rate (FDR). The criteria for differentially expressed genes (DEGs) were set as $FC \geq 2$ or ≤ 0.5 and $FDR \leq 0.05$. RBP genes were collected from public databases (<http://rbpdb.ccbr.utoronto.ca/>).

Normalization, Dimensionality Reduction, and Cell Clustering

The “NormalizeData” function in Seurat was used to normalize gene expression matrices using the default logarithmic normalization technique. The “FindVariableFeatures” function was used to identify highly variable genes. The scaled expression matrix was then used for principal

component analysis (PCA), and the top 50 principal components were chosen for further examination. Cellular heterogeneity was shown, and nonlinear dimensionality was reduced using uniform manifold approximation and projection (UMAP). Using a graph-based clustering technique using the “FindNeighbors” and “FindClusters” functions, cell clustering was carried out. In order to get cellular subpopulations of biological significance, cluster resolution parameters were tuned. For the main clustering of all cells, the cluster resolution parameter was set to 0.6. For subsequent sub-clustering of KC/DC/T cells, a resolution of 0.3 was applied to identify finer subpopulations within these major cell types. Based on RBP, the clustering resolution is 0.4, the resolution of the KC/DC/T cell sub-clustering is 0.4.

Cell Type Annotation

The scType technique was used in conjunction with previously identified marker genes linked to psoriasis skin tissues to perform cell type annotation [19]. Major cell populations, including KCs, DCs, T cells, NK cells, melanocytes, fibroblasts, endothelial cells, and other immune cell populations, were identified according to canonical marker gene expression patterns. Representative marker genes for each cell type were visualized using heatmaps and feature plots.

RBP-Based Clustering Analysis

To characterize RBP-associated transcriptional programs, unsupervised clustering analysis was performed based exclusively on the expression profiles of the RBP genes. Dimensionality reduction and clustering analyses were conducted using Seurat as described above. Distinct RBP-related clusters (R_clusters) were identified and visualized using UMAP. The proportions of different RBP expression subsets among healthy and psoriasis samples and among distinct cell types were further quantified and compared.

Differential Gene Expression Analysis

Differentially expressed genes (DEGs) between healthy and psoriasis groups were identified using the “FindMarkers” function in Seurat for scRNA-seq data and the DESeq2 package (version 1.40.2) for bulk RNA-seq data. Genes with $|\log_2 \text{ fold change}| > 0.25$ and adjusted p -value < 0.05 were considered significantly differentially expressed in scRNA-seq analyses. For bulk RNA-seq analyses, genes with $|\log_2 \text{ fold change}| > 1$ and p -value < 0.05 were considered significant. Differentially expressed RBP genes were extracted for subsequent analyses. Volcano plots and heatmaps were generated using the ggplot2 (version 3.4.2, <https://ggplot2.tidyverse.org/>) and pheatmap (version 1.0.13, <https://cran.r-project.org/package=pheatmap>) packages in R.

Construction of RBP Candidate Association Networks

To investigate the regulatory functions of RBPs, co-expression network analysis was performed using the pySCENIC workflow (version 0.12.1, <https://github.com/artslab/pySCENIC>). Differentially expressed RBP genes identified in KC, DC, and T cells were used as candidate regulators. The pySCENIC GRNBoost2 algorithm was applied to infer coexpression relationships between RBPs and their potential candidate genes. Importance scores generated by pySCENIC were used to identify highly confident RBP-candidate gene pairs. Gene pairs with importance values > 60 were retained for downstream analyses. Cytoscape software (version 3.9.1, <https://cytoscape.org>) was subsequently used to construct and visualize RBP-candidate association networks.

Functional Enrichment Analysis

Gene Ontology (GO) enrichment analyses were performed using the clusterProfiler package (version 4.8.1, <https://bioconductor.org/packages/clusterProfiler/>) in R. Biological process enrichment analyses were conducted for RBP candidate genes and alternative splicing-associated genes. Pathways with p -value < 0.05 were considered significantly enriched.

Cell-Cell Communication Analysis

Intercellular communication networks were analyzed using the CellChat package (version 1.6.1, <https://github.com/sqjin/CellChat>). CellChat was applied to infer ligand-receptor interactions among KCs and immune cell populations in healthy and psoriatic skin samples. Communication probabilities and signaling pathway strengths were calculated based on known ligand-receptor interaction databases integrated within CellChat. The numbers and strengths of interactions between different RBP-associated cellular subsets were compared between healthy and psoriasis groups. Differential signaling pathways and ligand-receptor pairs were further identified and visualized using heatmaps, bubble plots, and network diagrams.

Alternative Splicing Analysis

Alternative splicing analyses were performed using the Splicing site Usage Variation Analysis (SUVA) pipeline [23]. This pipeline identifies and quantifies five types of splicing events, including four Near-Intron Retained (NIR) types (alt3p, alt5p, olp, contain) as well as Intron Retention (ir). Regulated alternative splicing (RAS) events were identified and quantified in healthy and psoriatic skin tissues. Splicing ratios for each RAS event were calculated to evaluate splicing alterations between groups. The reads per splice junction were obtained using HISAT2 (v.2.2.1) alignment. RAS events were defined as those with a $p \leq 0.05$ and $|\text{Differential Splicing Ratio}| \geq 0.15$. Additionally, only events with a percentage of spliced reads (pSAR) of at

least 50% in either condition were retained for further analysis. PCA based on RAS splicing ratios was performed to assess global splicing pattern differences between healthy and psoriasis samples. Heatmaps were generated to visualize significantly altered RAS events.

Correlation Analysis Between RBPs and Alternative Splicing Events

To explore the potential regulatory relationships between RBPs and alternative splicing events, correlation analyses were performed between differentially expressed RBPs and RAS events identified from bulk RNA-seq data. Subsequently, Spearman's rank correlation coefficients were calculated using R. RBP-RAS pairs with absolute correlation coefficients ≥ 0.95 and p -values ≤ 0.01 were considered significantly associated. Functional enrichment analysis was subsequently conducted for genes involved in significantly correlated RAS events to identify biological processes potentially regulated by RBPs.

Results

ScRNA-seq Transcriptomic Profiling Reveals Cellular Heterogeneity and Distinct RBP Signatures in Psoriatic Skin

We examined single-cell transcriptome profiles from psoriatic lesions and healthy skin using the GSE151177 dataset in order to describe the cellular environment and RBP regulatory characteristics in psoriasis [19]. Following quality inspection, 22228 high-quality single cells were retained for further examination, which identified 11 primary cell types and 15 different cell clusters (Fig. 1A). **Supplementary Fig. 1A** displays representative marker genes for each kind of cell. Changes were observed in psoriatic skin when comparing cellular composition. In healthy skin, KCs were the predominant cell population, whereas psoriatic lesions showed lower proportions of KCs along with a noticeable concentration of T cells and DCs (Fig. 1B), consistent with the inflammatory features of psoriasis. We examined the expression patterns of 2141 known RBP genes to better understand RBP-associated transcriptional heterogeneity. We found 13 different RBP-related clusters (R_clusters) (Fig. 1C). Different cell populations showed distinct RBP fingerprints. While T cells and NK cells exhibited highly similar RBP expression profiles, semimature and mature DCs showed clearly distinct RBP expression patterns. Furthermore, variation was observed among different KC subtypes (**Supplementary Fig. 1B**). R12 was enriched in semimature DCs from psoriatic lesions compared with healthy skin, whereas R9 showed preferential expression in mature DCs. R4 and R11 were predominantly abundant in immune cell types, such as T cells and NK cells. R7 and R8 expression was elevated in basal KCs, whereas R2 and R6 were enriched in corneum KCs. In psoriasis samples, granulosum KCs had increased expression of R6 and

R8, whereas spinosum KCs revealed upregulation of R2, R6, and R8 (Fig. 1D). Globally, psoriatic lesions were dominated by R0 and R2, while healthy skin was dominated by R1 and R5 (**Supplementary Fig. 1C,D**). The presence of cell type-specific RBP regulatory mechanisms in psoriatic skin was highlighted by the extremely distinct RBP expression profiles that each cellular subset displayed (Fig. 1E).

Single-Cell Analysis Reveals Heterogeneity and Regulatory Modules of Cell-Specific RBPs in Psoriatic KCs

To investigate the expression patterns of RBPs in KCs and their alterations in psoriasis, we analyzed the expression profiles of 2141 reported RBP genes and identified 10 distinct RBP-related clusters within KCs (Fig. 2A). The composition of these RBP expression subsets differed between healthy skin and psoriatic lesions (Fig. 2B). In particular, RBP expression programs were strongly associated with disease status, with R0, R2, and R3 predominantly enriched in healthy samples, whereas R1, R5, and R6 were predominant in psoriasis samples (Fig. 2B). Differential expression analysis identified several RBPs that were dysregulated in psoriatic KCs. Among them, cystatin B (CSTB), N-myc downstream-regulated gene 1 (NDRG1), lactate dehydrogenase A (LDHA), aldolase A (ALDOA), histone cluster 1 H1 family member c (HIST1H1C), calcium-regulated heat-stable protein 1 (CARHSP1), and tumor protein, translationally-controlled 1 (TPT1) were upregulated, whereas alpha-2-glycoprotein 1, zinc-binding (AZGP1), ZFP36 zinc finger CCCH-type (ZFP36), ribosomal protein S6 (RPS6), ribosomal protein S8 (RPS8), ribosomal protein S10 (RPS10), ribosomal protein S14 (RPS14), ribosomal protein S17 (RPS17), ribosomal protein L13a (RPL13A), nucleophosmin 1 (NPM1), and DEXD/H-box helicase 39A (DDX39A) were downregulated in psoriasis samples compared with healthy controls (Fig. 2C). To further elucidate the regulatory roles of RBPs in psoriatic KCs, co-expression analysis was performed to identify putatively associated genes correlated with differentially expressed RBPs. A candidate association network consisting of RBPs and their highly correlated genes was subsequently constructed (Fig. 2D). Functional enrichment analysis revealed that genes highly associated with AZGP1, desmoplakin (DSP), S100 calcium-binding protein A9 (S100A9), CSTB, and ribonuclease 7 (RNASE7) were significantly associated with keratinization, KC differentiation, and epidermal development pathways (Fig. 2E). In contrast, genes associated with TPT1, thymosin beta 4 X-linked (TMSB4X), and major histocompatibility complex class I, A (HLA-A) were enriched in immune response-related pathways, including antigen processing and presentation and interferon-mediated signalling. Moreover, genes associated with ZFP36 and Zinc finger CCCH-type containing 12A (ZC3H12A) were primarily involved in inflammatory response pathways and cellular responses to lipopolysac-

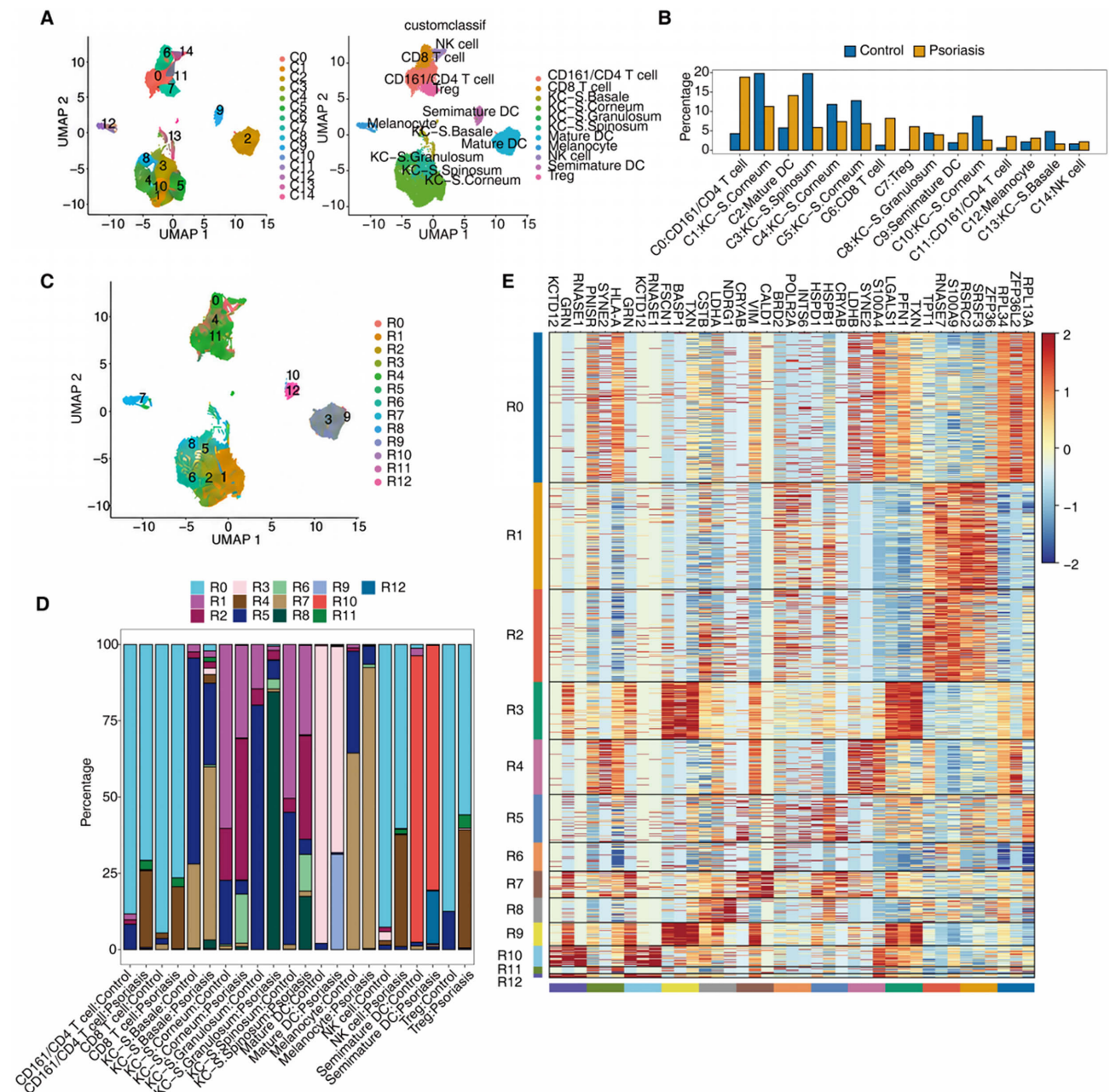


Fig. 1. Single-cell transcriptomic landscape and RNA-binding proteins (RBPs)-based clustering in healthy and psoriatic skin. (A) Uniform manifold approximation and projection (UMAP) visualization; a total of 15 cell clusters were identified. (B) Comparison of the relative proportions of major cell clusters across healthy and psoriatic samples. (C) UMAP plot showing 13 distinct clusters identified by unsupervised clustering based on RBP gene expression profiles alone (RBP expression subsets, R0–R12). (D) Comparison of the proportions of RBP expression subsets across different cell types between healthy and psoriasis groups. (E) Heatmap showing the expression patterns of representative marker genes across each RBP expression subset.

charide stimulation (Fig. 2E). In addition, pathways related to translation and tumour necrosis factor-associated apoptosis were significantly enriched in psoriasis-associated KCs (Fig. 2E). UMAP visualization further demonstrated that RBPs involved in keratinization-related pathways, including DSP, S100A9, CSTB, and RNASE7, were up-regulated in psoriatic lesions compared with healthy skin (Supplementary Fig. 2A–D). All of these results show that

KCs in psoriatic skin undergo substantial RBP-mediated transcriptional reprogramming, which may contribute to aberrant keratinization, inflammatory activation, apoptosis, self-antigen presentation, and subsequent immune cell recruitment during psoriasis progression.

transferase pi 1 (GSTP1)- and RNASE1-associated targets were primarily involved in immune system processing pathways (**Supplementary Fig. 3B**). We next characterized RBP expression patterns in T cells and observed alterations in the composition of RBP-related clusters between healthy and psoriatic samples (Fig. 3D,E). In healthy skin, R0 represented the dominant RBP cluster, whereas R0, R1, and R2 were enriched in psoriatic lesions (Fig. 3E), suggesting dynamic remodeling of RBP-associated transcriptional programs during psoriasis progression. Several RBPs were dysregulated in psoriatic T cells. Up-regulated genes included Ly1 antibody reactive homolog (LYAR), ZFP36 ring finger protein like 1 (ZFP36L1), lactate dehydrogenase B (LDHB), CSTB, small nuclear ribonucleoprotein U5 subunit 200 (SNRNP200), filamin A (FLNA), ubiquitin conjugating enzyme E2 M (UBE2M), DExD/H-box helicase 17 (DDX17), coronin 1A (CORO1A), and calcium-regulated heat-stable protein 1 (CARHSP1), whereas HSPB1, CRYAB, ribosomal protein S4 Y-linked 1 (RPS4Y1), RPS26, HSPA1A, heat shock protein family Hsp90 beta member 1 (HSP90AB1), ubiquitin C (UBC), SRSF3, ribosomal protein L31 (RPL31), and DNAJA1 were significantly downregulated (Fig. 3F). Co-expression relationship analysis further revealed extensive co-expression relationships between RBPs and their putative associated genes in T cells (**Supplementary Fig. 3C**). Functional enrichment analysis indicated that genes associated with HLA-A and LYAR were significantly enriched in immune response pathways, including antigen processing and presentation and interferon signalling pathways (**Supplementary Fig. 3D**). Collectively, these findings demonstrate that both DCs and T cells undergo extensive RBP-mediated transcriptional reprogramming in psoriasis, which may contribute to immune system processing, antigen presentation, inflammatory signalling, and sustained immune activation during disease progression.

Intercellular Signaling Between KCs and Immune Cell Subsets Shows Dramatic Changes

To elucidate the potential interactions among RBP-expressing cell subsets during psoriasis progression, we systematically analyzed intercellular communication networks between KCs and immune cells. The number and strength of interactions between KC-associated RBP subsets and immune cells (Fig. 4A) and between immune cell-associated RBP subsets and KCs (**Supplementary Fig. 4A**) were greater in psoriatic lesions than in healthy skin, suggesting extensive remodeling of cell-cell communication during disease development. Further analysis of signaling transmission and reception revealed significant changes in communication activity among specific RBP expression subsets. In KCs, the R5, R6, R7, and R8 subsets showed enhanced signal-sending and/or signal-receiving capacities in psoriasis samples compared with healthy controls. Similarly, mature DCs, CD4⁺ T cells, CD8⁺ T cells,

and Treg cells exhibited increased communication activity in psoriatic lesions (Fig. 4B). In addition, immune cell-associated RBP subsets, particularly R1, R4, R6, R7, R8, and R9, showed significantly elevated interactions with different KC subtypes in psoriasis, accompanied by enhanced signalling exchange among KC populations themselves (**Supplementary Fig. 4B**).

Heatmap analysis further demonstrated globally increased interaction numbers and interaction strengths between KC-associated RBP subsets and immune cells (Fig. 4C), as well as between immune-associated RBP subsets and KCs (**Supplementary Fig. 4C**). Analysis of overall information flow across signalling pathways identified several pathways with substantially altered activity in psoriatic lesions compared with healthy skin (Fig. 4D). Ligand-receptor interaction analysis revealed multiple psoriasis-specific signalling events. Notably, major histocompatibility complex class (MHC)-I signalling derived from the R5 subset specifically targeted CD8⁺ T cells, whereas MHC-II signalling from the R5 subset interacted with semimature DCs exclusively in psoriasis samples. Moreover, the R9 subset exhibited enhanced signalling through MHC-I, MHC-II, C-C motif chemokine ligand (CCL), lymphocyte-specific protein tyrosine kinase (LCK), and galectin family proteins (Galectin), CD99, and CD45 pathways toward multiple immune cell populations, including CD4⁺ T cells, CD8⁺ T cells, semimature and mature DCs, and Treg cells (Fig. 4E,F). Several signalling pathways were upregulated in psoriasis, including macrophage migration inhibitory factor (MIF) signalling derived from the R1 and R3 subsets toward multiple immune cell populations and MHC-I signalling from the R9 subset toward CD8⁺ T cells. In contrast, MHC-I signalling from the R0, R2, R4, and R7 subsets to CD8⁺ T cells was reduced in psoriatic lesions. In addition, MIF, amyloid precursor protein (APP), and CD99 signalling derived from the R7 subset toward multiple immune cell populations was decreased (Fig. 4E,F). Together, these results suggest that RBP-associated transcriptional processes in KCs alter intercellular communication networks in psoriasis and may be crucial in regulating inflammatory response and immune cell activation during disease progression.

Integration of Bulk RNA-Seq Data Revealed That Extensive Alternative Splicing in Psoriasis May Be Associated With Dysregulated RBPs

RBPs play key roles in posttranscriptional regulation, including selective splicing, mRNA stabilization, and translational control, thereby contributing to the expression of cell-specific functional proteins. To investigate the potential involvement of RBPs in alternative splicing regulation during psoriasis progression, we further analyzed bulk RNA-sequencing data derived from normal skin and psoriatic lesions (PRJNA481993), as full-length splicing information could not be reliably obtained from 10× single-

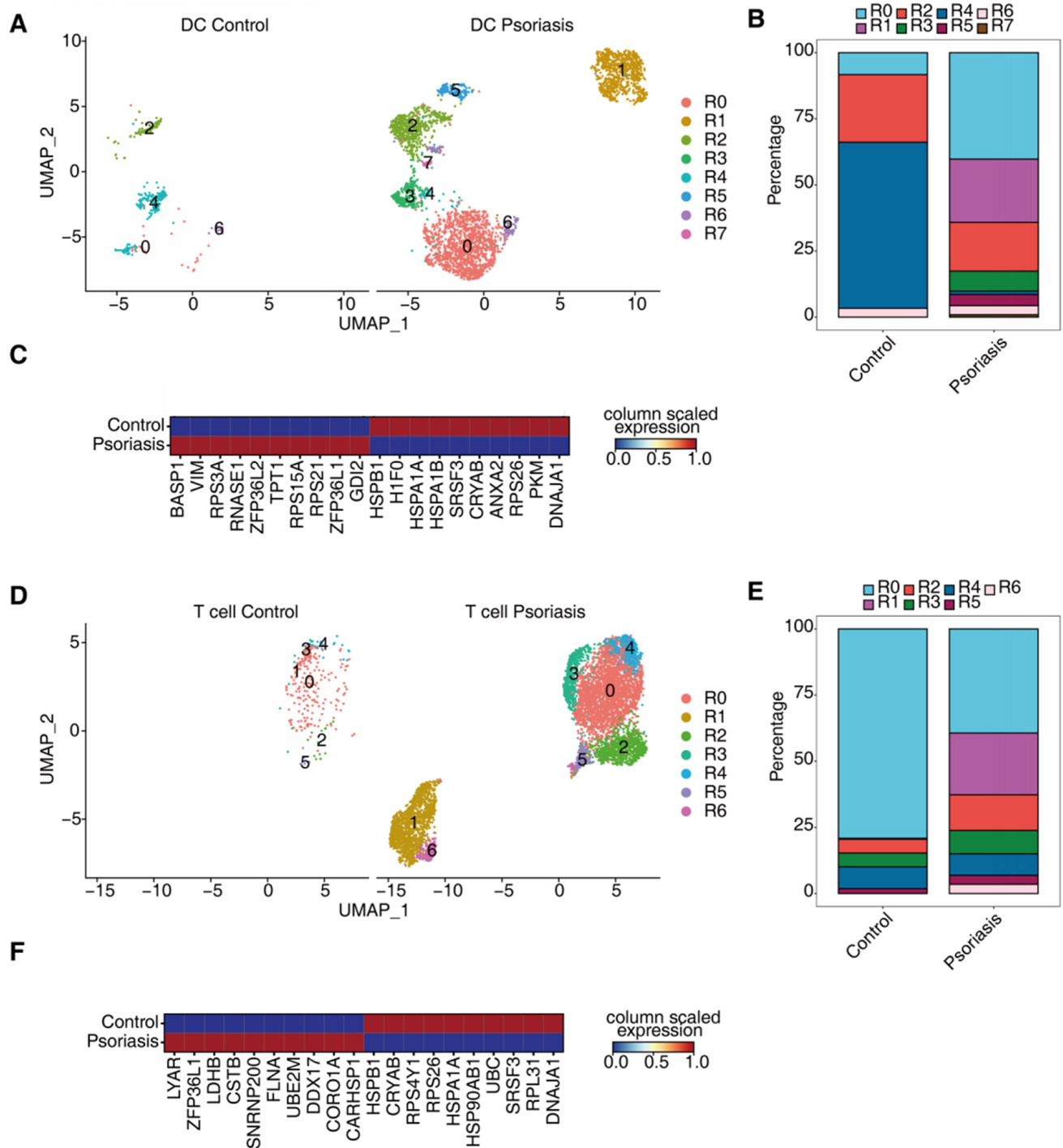


Fig. 3. RBP expression-based clustering and differential RBP signatures in dendritic cells (DCs) and T cells in healthy and psoriatic skin. (A) UMAP plot showing eight clusters identified by unsupervised clustering of DCs based on RBP gene expression (RBP expression subsets, R0-R7). (B) Comparison of the relative proportions of each RBP expression subset in DC across healthy and psoriasis samples. (C) Heatmap showing the top differentially expressed RBPs in DC between psoriasis patients and healthy controls. Blue represents significantly downregulated genes, and red represents significantly upregulated genes. (D) UMAP plot showing seven clusters identified by unsupervised clustering of T cells based on RBP gene expression alone (RBP expression subsets, R0-R6). (E) Comparison of the relative proportions of each RBP expression subset in T cells across healthy and psoriasis samples. (F) Heatmap showing the top differentially expressed RBPs in T cells between psoriasis patients and healthy controls. Blue represents significantly downregulated genes, and red represents significantly upregulated genes.

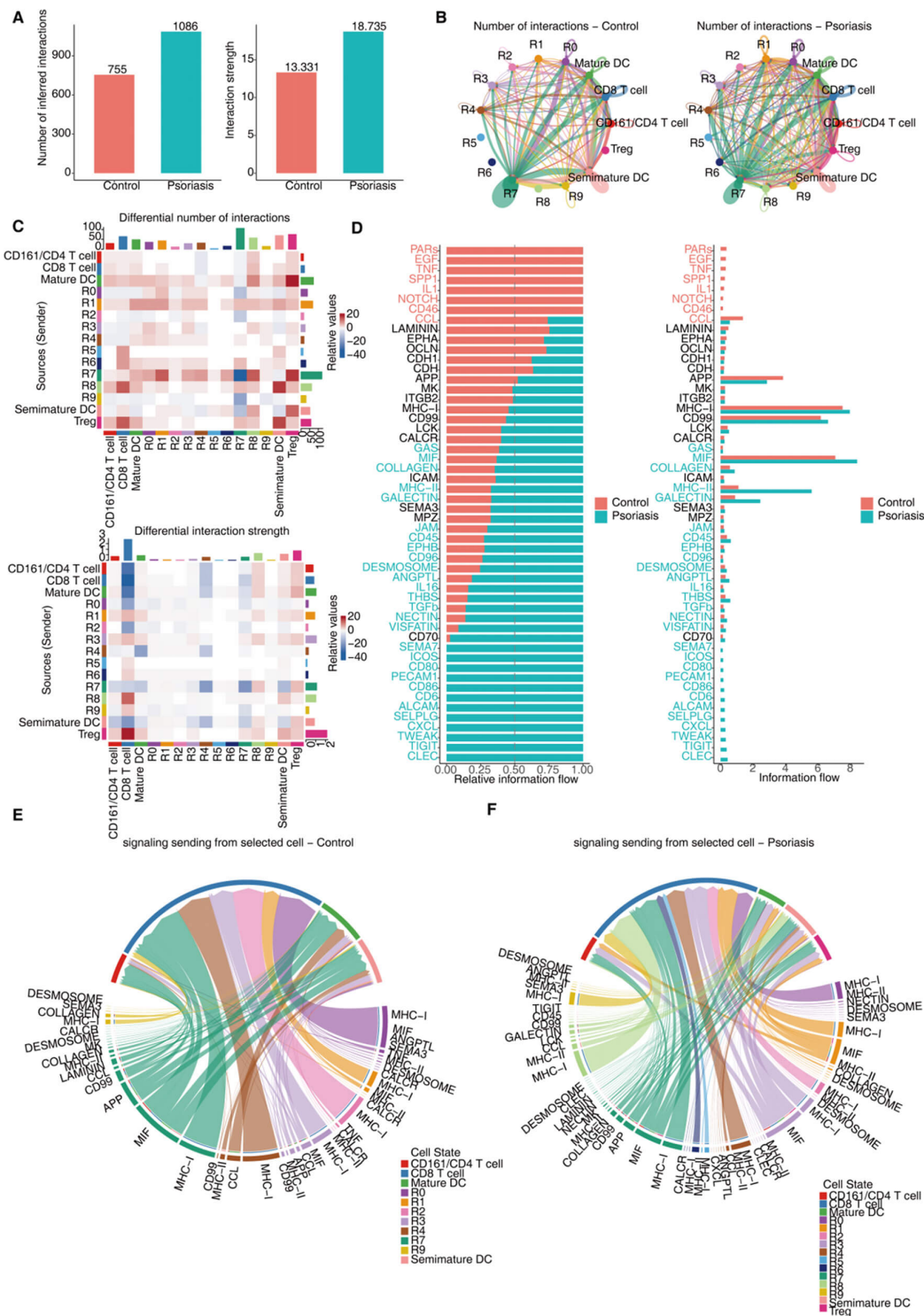


Fig. 4. Cell-cell communication analysis of RBP-associated cellular subsets in healthy and psoriatic skin. (A) Bar plot showing the total number and interaction strength of inferred cell-cell communication networks in healthy and psoriasis groups. (B) CellChat-based analysis of signaling interactions between KC RBP subsets and immune cell populations across healthy and psoriatic samples. (C) Heatmap showing the number and strength of interactions between KC-derived RBP subsets and immune cells. (D) Comparison of global signaling pathway activity based on overall information flow inferred by CellChat in healthy and psoriasis groups; red and blue indicate pathway activity in healthy and psoriatic samples, respectively. (E,F) Chord diagrams illustrating representative ligand-receptor interactions specific to healthy and psoriatic conditions.

cell sequencing data. Differential expression analysis between healthy and psoriatic skin tissues identified 4496 DEGs, including 197 dysregulated RBP genes (Fig. 5A). **Supplementary Fig. 5A** illustrates the expression profiles of RBPs. Integrative analysis identified 48 overlapping differentially expressed RBPs shared between the bulk RNA-seq and single-cell RNA-seq datasets, further supporting the robustness of RBP dysregulation in psoriasis (**Supplementary Fig. 5B**). The SUVA method was used to evaluate RAS events in order to fully describe alternative splicing modifications. Hundreds to thousands of significantly different RAS events were found between the healthy and disease groups, indicating widespread splicing dysregulation in psoriatic lesions (**Supplementary Fig. 5C,D**). The RNA splicing landscape underwent significant remodeling during the development of psoriasis, as demonstrated by the unambiguous separation of healthy and psoriatic samples using principal component analysis based on RAS splicing ratios (**Supplementary Fig. 5E**). Fig. 5B shows the distribution of RAS splicing ratios between the two groups. Genes undergoing differential alternative splicing were found to be significantly enriched in pathways associated with chromatin remodeling, actin cytoskeleton organization, and mRNA processing (**Supplementary Fig. 5F**) according to functional enrichment analysis, indicating extensive changes in cellular structural and transcriptional regulatory mechanisms in psoriasis. Co-expression analysis was carried out by combining bulk RNA-seq-derived RBP expression profiles with RAS events identified from bulk RNA-seq datasets to investigate the potential regulatory associations between RBPs and alternative splicing events. After rigorous correlation filtering, biological processes such as cellular response to hydrogen peroxide, regulation of focal adhesion assembly, actomyosin structure organization, regulation of embryonic development, cell migration and cell-cell adhesion were found to be enriched in RAS-associated genes that were significantly correlated with dysregulated RBPs (Fig. 5C,D). Together, these results show that psoriasis is marked by widespread changes in alternative splicing and extensive RBP dysregulation, indicating a potential involvement of aberrant RBP-mediated posttranscriptional regulation may be involved in immunological dysfunction and pathological remodeling during the course of psoriasis.

Discussion

In this study, we integrated single-cell and bulk transcriptomic datasets to systematically dissect the cellular heterogeneity and RBP-centered regulatory architecture in psoriatic skin. A major finding of this study is that RBPs are not uniformly dysregulated across cell types, but instead form highly structured, cell-specific expression programs that are tightly associated with disease status. By combining RBP-based clustering, intercellular communication

analysis, and alternative splicing profiling, our results reveal a previously underappreciated layer of posttranscriptional regulation that may coordinate both immune activation and KC dysfunction in psoriasis.

Strong cell-type specificity and dynamic remodeling of RBP expression subgroups under psoriatic circumstances are noteworthy findings of the current investigation. A clear transition from homeostatic RBP programs in healthy skin to RBP modules linked to inflammation in lesions was observed in KCs. This result is in line with growing evidence that RBPs have the ability to directly control KC functional states. For example, it has been demonstrated that SRSF1 contributes to psoriatic pathogenesis and controls KC proliferation in HaCaT cells [24]. Furthermore, PPAR α -FADS2-mediated fatty acid metabolism remodeling [25] and keratin 17- α -enolase interaction-driven proliferation [26] are two examples of how metabolic and structural reprogramming of KCs has been linked to disease development. All of these findings provide credence to the idea that coordinated posttranscriptional regulatory reprogramming, as opposed to discrete transcriptional dysregulation, is closely associated with KC dysfunction in psoriasis. Our findings supported this idea by showing that keratinization, differentiation, and inflammatory signaling pathways were highly enriched in KC-associated RBP clusters in psoriasis. This implies that, rather than only serving as downstream effectors of inflammatory signals, RBPs may actively contribute to altering the identity and function of epithelial cells. The enrichment of immune-related regulatory programs within KC RBP networks further supports that epithelial cells may develop immune-like functional characteristics under inflammatory conditions. This process would strengthen bidirectional communication between KCs and immune cells and prolong chronic inflammation.

Immune cell types, especially DCs and T cells, also showed a similar disease-associated remodeling of RBP programs. We found a shift in DCs toward RBP signatures associated with antigen processing and immunological activation. This finding is consistent with previous research showing that different subsets of dendritic cells (DCs) contribute to the pathophysiology of psoriasis by suppressing IL-17A-driven inflammation via STING [27]. Furthermore, a previous study has shown that CCR7+ DC populations expressing IL-23A and IL-12B may promote disease recurrence [28]. Our research revealed additional connections between immune response, antigen processing pathways, and DC-associated RBP signatures, indicating that RBPs may regulate DCs' ability to deliver antigens and their inflammatory polarization. RBP changes were predominantly associated with programs related to antigen presentation and interferon signaling in T cells. RBPs may play a role in the stepwise coordination of immune activation within the psoriatic milieu, according to this cell-specific functional partitioning between DCs and T cells.

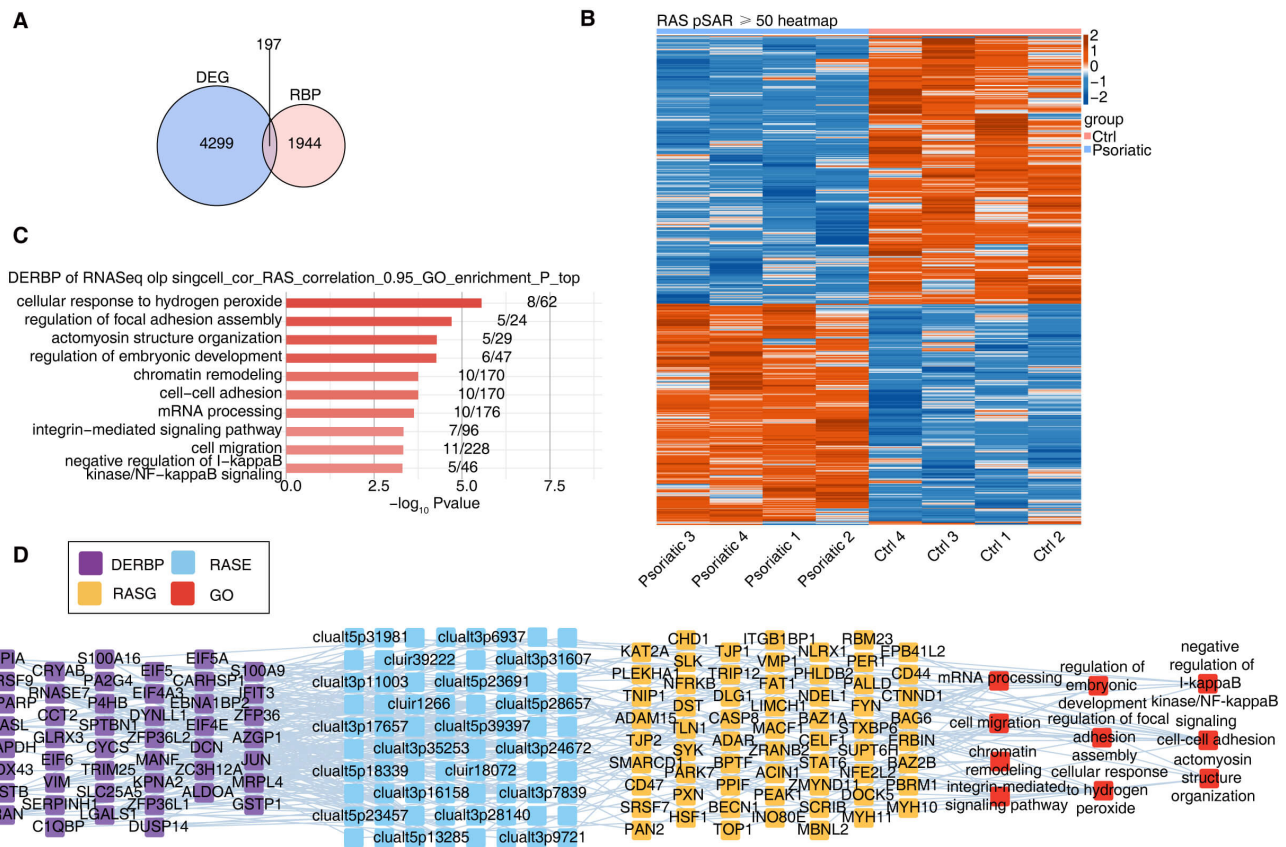


Fig. 5. Integrated analysis of differentially expressed RBPs and alternative splicing alterations in psoriasis. (A) Identification of differentially expressed RBPs between healthy and psoriatic samples based on bulk RNA-seq data (PRJNA481993). (B) Heatmap showing the splicing ratios of regulated alternative splicing (RAS) events in healthy and psoriatic skin samples. (C) GO enrichment analysis of genes associated with differentially expressed RBP-correlated alternative splicing events identified by integrating bulk RNA-seq and scRNA-seq datasets. (D) Integrated network illustrating relationships among differentially expressed RBPs, differentially expressed genes, alternative splicing events, and GO-enriched functional pathways in psoriasis.

Crucially, the coordinated remodeling of RBP programs across immunological and epithelial compartments implies that psoriasis entails a system-level reconfiguration of post-transcriptional regulatory networks in addition to cytokine-centered transcriptional reprogramming. RBPs may act as convergent regulators by incorporating inflammatory inputs into cell-type-specific functional outputs, as shown by these parallel changes across multiple cell types.

Psoriasis is characterized by excessive KC proliferation, aberrant differentiation, and ongoing immunological dysregulation from the standpoint of disease biology [29,30]. Signaling and metabolic pathways are crucial for these activities, according to recent data. For instance, lysophosphatidylcholine stimulates T cell differentiation and KC activation via glycolytic reprogramming [31]. KC hyperproliferation and the generation of inflammatory cytokines are influenced by CK2-mediated control of STAT3 and Akt signaling [31]. Furthermore, FBP1 controls KC proliferation and differentiation by epigenetic regulation of histone acetylation [32]. By showing that KC-associated RBPs are closely connected to keratinization, differentia-

tion, and inflammatory signaling pathways, our research expands this regulatory framework and suggests that post-transcriptional regulation adds another level of control in epithelial dysfunction.

Finally, our integrative study revealed a broad correlation between dysregulated RBPs and changes in alternative splicing (AS) in psoriatic skin. This is in line with growing evidence that RBP-mediated splicing control functions in psoriasis; GNL3 has been shown to affect the distribution of alternative splicing events [33]. Additionally, it has been demonstrated that KC-specific long non-coding RNAs control alternative splicing in epidermal differentiation programs [34]. A broad reconfiguration of the RNA splicing landscape in disease is shown by the fact that RBP-associated splicing events were sufficient in our analysis to discriminate psoriatic from healthy samples. Notably, RBP-driven splicing regulation extends beyond transcript abundance control to structural and nuclear regulatory systems, as seen by the high enrichment of genes impacted by differential splicing in cytoskeletal organization, chromatin remodeling, and RNA processing pathways. The idea that

RBP function as upstream regulators of transcript isoform variety in psoriasis is supported by the high connection between dysregulated RBPs and RAS events. Mechanistically, this RBP-splicing coupling might represent a feedback regulatory loop in which RBPs generated by inflammation modify splicing programs, changing the composition of protein isoforms and cell behavior. In the immunological and epithelial compartments, where quick functional adaptability is necessary, such a mechanism would be especially pertinent. Additionally, the preponderance of endocytosis and cytoskeleton-related pathways among RBP-associated splicing targets points to potential effects on immunological synapse formation, cellular motility, and antigen uptake, all of which could contribute to the progression of disease at multiple functional levels.

Despite providing a thorough single-cell multi-omics analysis of RBP-candidate association networks in psoriatic skin, several limitations should be noted. First, the majority of the transcriptome datasets used in this study are publicly accessible. Even though we combined bulk and single-cell RNA-seq data to increase robustness, the results are still mostly computational and need more experimental confirmation. Lastly, without incorporating other omics layers, such as proteomics, epigenomics, or spatial transcriptomics, this work focuses primarily on transcriptomic and posttranscriptional regulation. Future multimodal research is required to provide a more thorough knowledge of RBP-mediated regulatory mechanisms in the skin microenvironment, given the established significance of spatial organization and protein-level regulation in psoriasis.

Conclusion

In conclusion, this study shows that RBPs undergo substantial reprogramming in psoriatic skin and exhibit pronounced cell type-specific expression patterns. Functional changes in KCs and immune cells, including keratinization, immunological activation, and antigen processing, are closely associated with these RBP-candidate association systems. Crucially, we show that RBP-defined cellular subgroups are related to extensive alternative splicing dysregulation and improved intercellular communication in psoriasis. All of these results point to RBPs as important regulators combining cellular crosstalk with posttranscriptional gene regulation in the psoriatic milieu, offering potential new therapeutic targets.

Availability of Data and Materials

The raw scRNA-seq and bulk RNA-seq data analyzed in this study are publicly available from the GEO database and SRA database. The data that support the findings of this study are not publicly available due to privacy restrictions but are available from the corresponding author upon reasonable request.

Author Contributions

YLJ and HJY designed the research study; JL and JC performed the research; MS collected and analyzed the data. MS was involved in drafting the manuscript and all authors were involved in revising it critically for important intellectual content. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.24976/Discover.Med.202638213.255>.

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