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ORIGINAL RESEARCH

The mRNA Expression Profile of Psoriatic Lesion Distinct from Non-Lesion

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Purpose: Psoriasis is a chronic recurring autoimmune skin disease with a complex etiology and chronic progression; however, its molecular mechanisms remain unclear.

Patients and Methods: We performed transcriptomic analysis to profile the mRNA expression of psoriatic lesions (PL) and non-lesion (NL) tissues from psoriasis patients along with normal skin from healthy donors. RT-qPCR was used to validate the mRNA expression profiles.

Results: A total of 237 differentially expressed genes were screened and identified by RNA sequencing. GO and KEGG analysis indicated that these DEGs were enriched in the PPAR signaling pathway and intermediate filament cytoskeleton. For PPAR signaling pathway, the expression of five genes, including ADIPOQ, AQP7, PLIN1, FABP4 and LPL, were all significantly decreased in psoriatic lesions compared to normal skin by RT-qPCR. There is a clear difference between psoriatic lesions and non-lesion in the expression of ADIPOQ, AQP7 and LPL. For intermediate filament cytoskeleton, including KRT27, KRT25, KRT71, KRT86 and KRT85 were significantly decreased in the psoriasis lesions, showing agreement with the RNA-seq data.

Conclusion: This study revealed a significant difference between the mRNA expression profiles of PL, NL tissue and normal skin.

Keywords: psoriasis, RNA-sequencing, PPAR signaling pathway, keratin

Introduction

Psoriasis is an autoimmune disease characterized by[1] erythema and scale lesions that[2,3] affects approximately 2–4% of the population. Although the exact pathogenesis of this disease has not yet been fully determined, it is thought to be a systemic disease as its pathogenesis and development are determined by[4,5] cellular immune disorders, genetic, environmental, and[6] infectious factors, and interaction between metabolic, environmental, and[7] genetic factors.[8] Psoriasis is a cytokine-driven skin disease in which lesions are caused by abnormal thickening of the epidermis and hyperproliferation of keratinocytes (KCs).[9,10] Transcriptome studies of psoriasis have been performed using large patient cohorts to understand how gene expression is altered at lesions compared to macroscopic normal skin.

Studies have found differences in the mRNA expression of many genes between psoriasis and normal individuals.[11] C-myc, c-fos, and c-jun transcripts were significantly induced over in vivo levels 2–4 h after organ culture of normal or psoriatic keratome biopsies, demonstrating that these genes can be highly expressed in the context of tissue injury.[12] Haptoglobin protein expression was also markedly increased in the 138 psoriasis group compared with in the normal groups. There are also many genes expression is down-regulated, such as[13] DUSP1,[14] SMAD2, TGFbeta receptor I.

However, the characteristic lesions of psoriasis only appear locally and are distinctly different from the adjacent skin both in appearance and histopathology, as shown in Figure 1. Therefore, there may be other factors that contribute toward the manifestation of erythema and scales in psoriatic lesions that are absent in adjacent skin.[15] Although Jabbari et al examined the coding psoriatic transcriptome of lesional and normal skin samples from psoriatic individuals, the study did not examine normal skin samples collected adjacent to the psoriatic lesions. To elucidate the factors that are specifically

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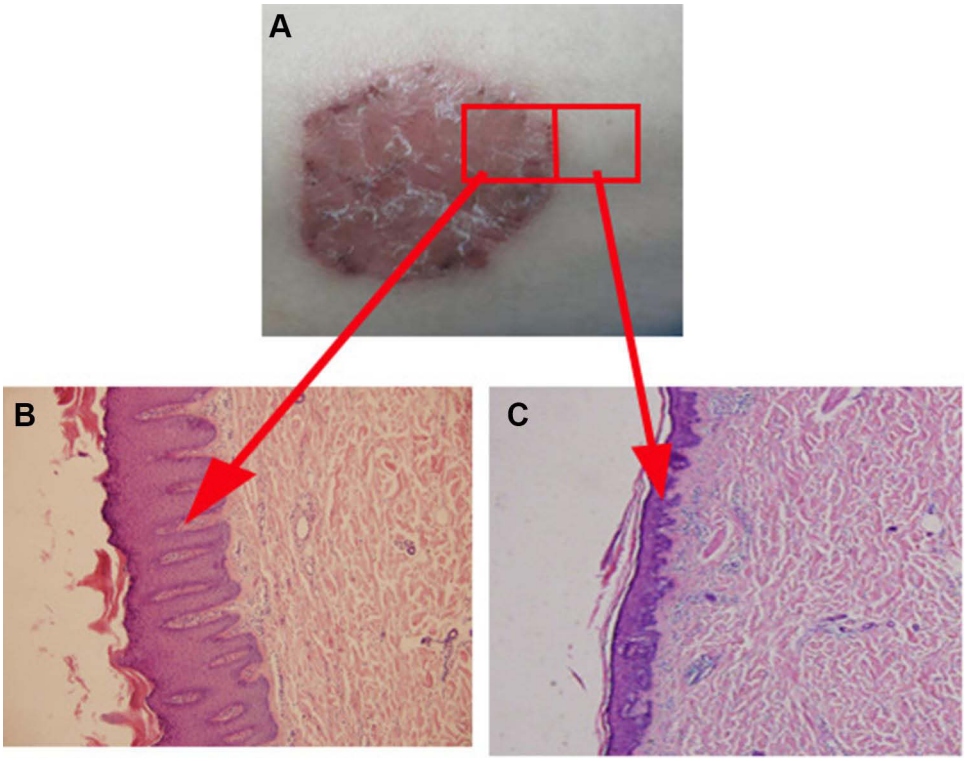

Figure 1 Psoriatic skin differs from adjacent skin in both appearance and histopathology. (**A**) The appearance of psoriasis patient; (**B**) Histopathology of psoriasis skin; (**C**) Histopathology of adjacent normal skin in psoriasis patient.

present in psoriatic lesions, our study provides a comprehensive mRNA profile of patients with psoriasis and directions for further study of the molecular mechanisms of psoriasis.

Materials and Methods

Samples

We collected 10 psoriatic lesions (PL) and adjacent normal skin (non-lesion, NL) samples from patients with psoriasis (five males and five females; 23–39 years-old) and 10 normal tissue samples from healthy volunteers (six males and four females; 25–40 years-old) from Taiyuan Central Hospital. All tissue specimens were stored at −80°C. All participants provided written informed consent and the study protocol was approved by the ethics committee of Taiyuan Central Hospital.

RNA Sequencing

Total RNA was extracted from tissues using TRIzol (Invitrogen, Carlsbad, CA, USA) and rRNA was depleted using a Ribo-Zero™ Magnetic Kit. RNA purity was checked using a KaiaoK5500® spectrophotometer (Kaiao, Beijing, China) and sequenced using an Illumina HiSeq 4000 platform on a 150 bp paired end run. Raw data was filtered to remove rRNA, low quality samples, linker contamination, and unknown base N content. The rRNA sequences were identified by mapping reads to the ribosome database with SOAP. Bowtie 2 was used to align the clean reads to the reference sequence and RSEM was used to calculate the number of reads mapping to genes.

DEG Analysis and Functional Analysis

Differential gene expression analysis was performed using the Limma R/Bioconductor software package in R (v. 3.22.7), which provides an integrated solution for both the differential expression and differential splicing analysis of RNA-seq data. The Benjamini–Hochberg method was used as an FDR adjustment for multiple testing correction. An FDR

threshold of < 0.05 was used to define statistical significance. Metascape (http://metascape.org) was used to perform gene enrichment and functional annotation analyses.

Real-Time Quantitative PCR (RT-qPCR)

RNA was extracted from the samples using Trizol (Invitrogen, Carlsbad, CA, USA) and RT-qPCR was performed on ten preselected psoriasis-related genes using the qPCR primers shown in Supplementary Table 1. Each RT-qPCR reaction was performed in duplicate and the mean threshold cycle (Ct) value for each sample was used for data analysis. The $2^{-\Delta\Delta Ct}$ method was used to determine the fold-change in expression level normalized to β-actin. Paired *t*-test analyses were performed on the $2^{-\Delta\Delta Ct}$ values to compare the two groups of samples.

Statistical Analysis

Statistical analyses were carried out using the R software package (http://cran.r-project.org/). Differences between the mRNA expression levels of patients with psoriasis and normal individuals were evaluated by paired t-tests. Statistical significance was set at $P < 0.05$.

Results

Genome-Wide mRNA Analysis of Psoriatic Lesion (PL) and Non-Lesion (NL)

To comprehensively determine the mRNA landscape of psoriasis, we profiled the mRNA expression of psoriatic lesion (PL) and non-lesion (NL) samples from patients with psoriasis by RNA sequencing. A total of 1.5–2.0 billion clean reads were obtained for each sample using hierarchical indexing for spliced alignment of transcripts (HISAT). Furthermore, we used CPC, txCdsPredict, pfam, and CNCI to assess transcription coding ability (Figure 2A), obtaining a total set of 187,731 transcripts (including 29,750 novel mRNAs) that were defined as candidate mRNAs (Figure 2B and C). We also quantitatively analyzed the mRNA expression levels for read counts and Fragments per Kilobase Million (FPKM), finding that most of the mRNAs contained over 10 exons with a transcript length of over 500 bp (Figure 2D). Moreover, we evaluated the transcription levels of the mRNAs. To investigate whether the differentially expressed mRNAs regulate genes and signaling pathways associated with psoriasis, we used target prediction programs to predict potential targets of the dysregulated mRNAs. Two hundred and thirty-seven differentially expressed mRNAs were identified through RNA-seq analysis. Among them, 164 were significantly upregulated, and 73 were significantly downregulated (Fold Change ≥2.0, P-value ≤ 0.05) (Figure 2E).

Signaling Pathway Enrichment Analysis

GO analysis revealed considerable functional overlap among the 237 predicted target genes and found that they were enriched in cellular components including lipid metabolic processes, small molecule metabolic processes, chemical homeostasis, and response to oxygen-containing compounds ($P < 0.05$), and in biological processes including extracellular region, extracellular space, and anchored membrane components (Figure 3A and B). KEGG-based pathway enrichment analysis was performed using the DAVID database and signaling pathways with $P < 0.05$ were selected. There was considerable overlap among the signaling transduction pathways of the target genes, with KEGG pathway analysis highlighting the peroxisome proliferator-activated receptor (PPAR) signaling pathway and arachidonic acid metabolism ($P < 0.05$; Figure 3C).

RT-qPCR Analysis Expression of Gene in Psoriatic Lesion (PL), Non-Lesion (NL) and Normal Skin(Nor)

According to RNA-seq analysis, we retrieved ten genes related to the peroxisome proliferator activated receptor (PPAR) signaling pathway and intermediate filament cytoskeleton (Figure 4A). These genes are down-regulated in psoriatic lesions compared with non-psoriatic lesions. To verify the RNA-seq results, we selected ten dysregulated mRNAs for RT-qPCR analysis. For PPAR signaling pathway, we selected five genes, including adipoq (ADIPOQ), aquaglyceroporin 7 (AQP7), fatty acid-binding protein (FABP4), lipoprotein lipase (LPL), and perilipin 1 (PLIN1), which were all

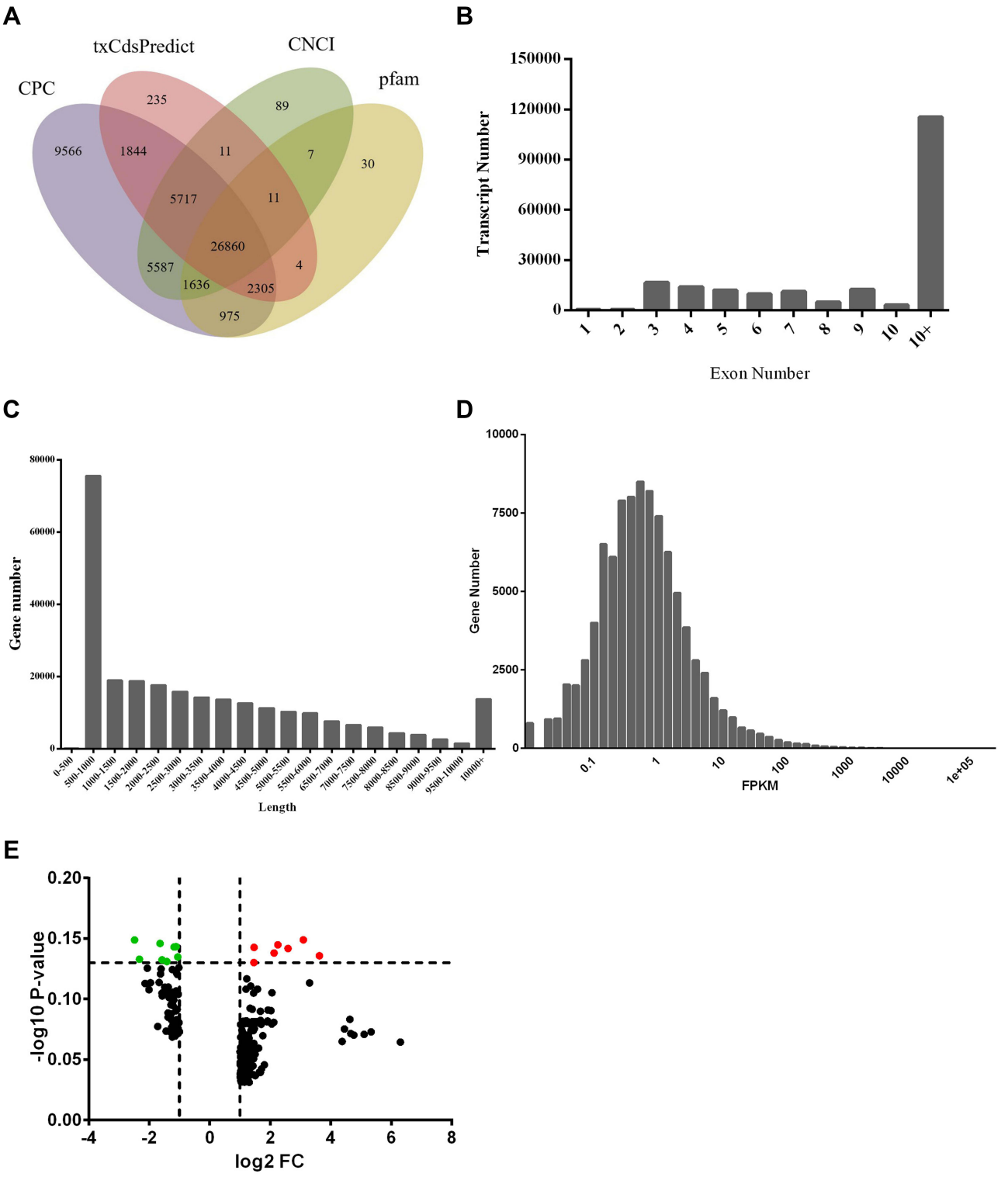

Figure 2 Genome-wide profiling of differentially expressed mRNAs. (**A**) Venn diagram of transcription coding ability prediction. (**B**) Distribution of exons. (**C**) Distribution of transcript length. (**D**) Histogram of transcription levels. (**E**) Volcano plot of differentially expressed mRNAs between psoriatic lesions (PL) and adjacent normal skin (NL).

significantly decreased in psoriatic lesions compared to normal skin by RT-qPCR (Figure 4C). There is a clear difference between psoriatic lesions and non-lesion in the expression of ADIPOQ, AQP7 and LPL. For intermediate filament cytoskeleton, including KRT27, KRT25, KRT71, KRT86 and KRT85 were significantly decreased in the psoriasis lesions, showing agreement with the RNA-seq data (Figure 4B).

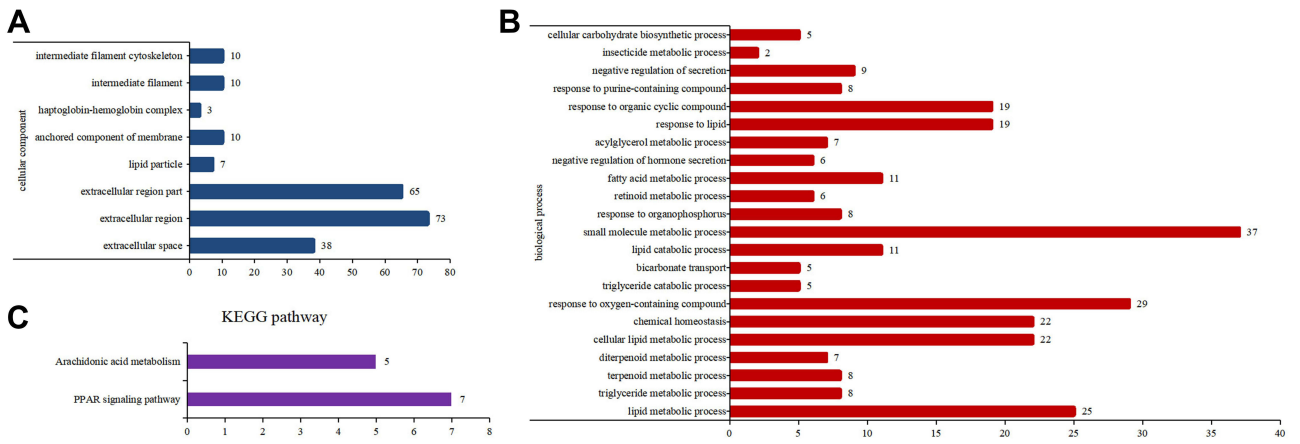

Figure 3 Gene Ontology (GO) and KEGG analysis of target genes. (**A**) GO biological process analysis. (**B**) GO cellular component analysis. (**C**) KEGG pathway analysis.

Discussion

Psoriasis is a clinically heterogeneous lifelong skin disease that presents in multiple forms such as[16,17] plaque, flexural, guttate, pustular or erythrodermic.[18] Psoriatic lesions result from complex interactions between dermal or epidermal cells, resident and infiltrating immune cells, and a variety of cytokines.[19] Psoriasis has differences in gene expression between lesions and non-lesions, such as atopic dermatitis and cutaneous lupus.[20,21] Previous studies have performed transcriptomic analyses to investigate molecular abnormities in patients with psoriasis. However, these studies have focused on skin lesions and therefore the transcriptomic signature of the peripheral circulation in psoriasis, a systematic autoinflammatory disease, remains largely unknown. In this study, we conducted an RNA-seq-based transcriptomic analysis of psoriatic lesions and adjacent normal skin, which may provide insights into the pathogenesis of psoriasis and potential biomarkers for its diagnosis and treatment.

Currently, many psoriasis-associated mRNAs have been investigated that may play an important role in susceptibility to psoriasis. To the best of our knowledge, this study determined the mRNA expression profiles of psoriatic lesions and adjacent normal skin. We identified 237 psoriasis-associated genes via multiple methods to provide a convincing set of genes for further enrichment and pathogenicity analyses. GO analysis was performed to investigate the biological functions that were enriched among the dysregulated mRNAs, revealing that differentially expressed mRNAs in psoriatic lesions and adjacent normal skin may be involved in the intermediate filament cytoskeleton, extracellular region, and fatty acid metabolic processes.

Interestingly, the intermediate filament cytoskeleton contained the differentially expressed genes KRT27, KRT25, KRT71, KRT86, and KRT85, which are known to be involved in the development of psoriasis. RT-qPCR revealed that KRT27, KRT25, KRT71, KRT86 and KRT85 expression were markedly higher in the normal control group compared with the psoriasis and NL groups, consistent with the RNA seq-analysis results.[22,23] Keratins (KRT) are the major components of the epithelial cytoskeleton and are responsible for maintaining the structural stability and integrity of keratinocytes.[24] Keratins also regulate keratinocyte mobility via cytoplasmic viscosity during stratification or wound healing, while[25] keratinocyte hyperproliferation is considered a hallmark of psoriasis.[26] K17 exerts both pro-proliferative and pro-inflammatory effects on keratinocytes. Moreover, K17 peptides trigger autoreactive T cells and promote psoriasis-related cytokine production. In this study, KRT27, KRT25, KRT71, KRT86 and KRT85 mRNA levels were observed in patients with psoriasis and may promote excessive keratinocyte proliferation,[27,28] consistent with psoriasis characterized by cornified layer-hyperkeratosis expansion.

Moreover, KEGG pathway analysis revealed considerable overlap between the signal transduction pathways of the target gene set, particularly the PPAR signaling pathway and arachidonic acid metabolism, suggesting that they may be closely related to the biosynthesis and metabolism of psoriasis and include ADIPOQ, AQP7, PLIN1, FABP4, and the expression of those genes were significantly decreased in the psoriasis group. Furthermore,[29–31] these genes are known participate in the PPAR signaling pathway.[32] Reducing the level of the PPARγ gene expression may be a result of the overregulation of several

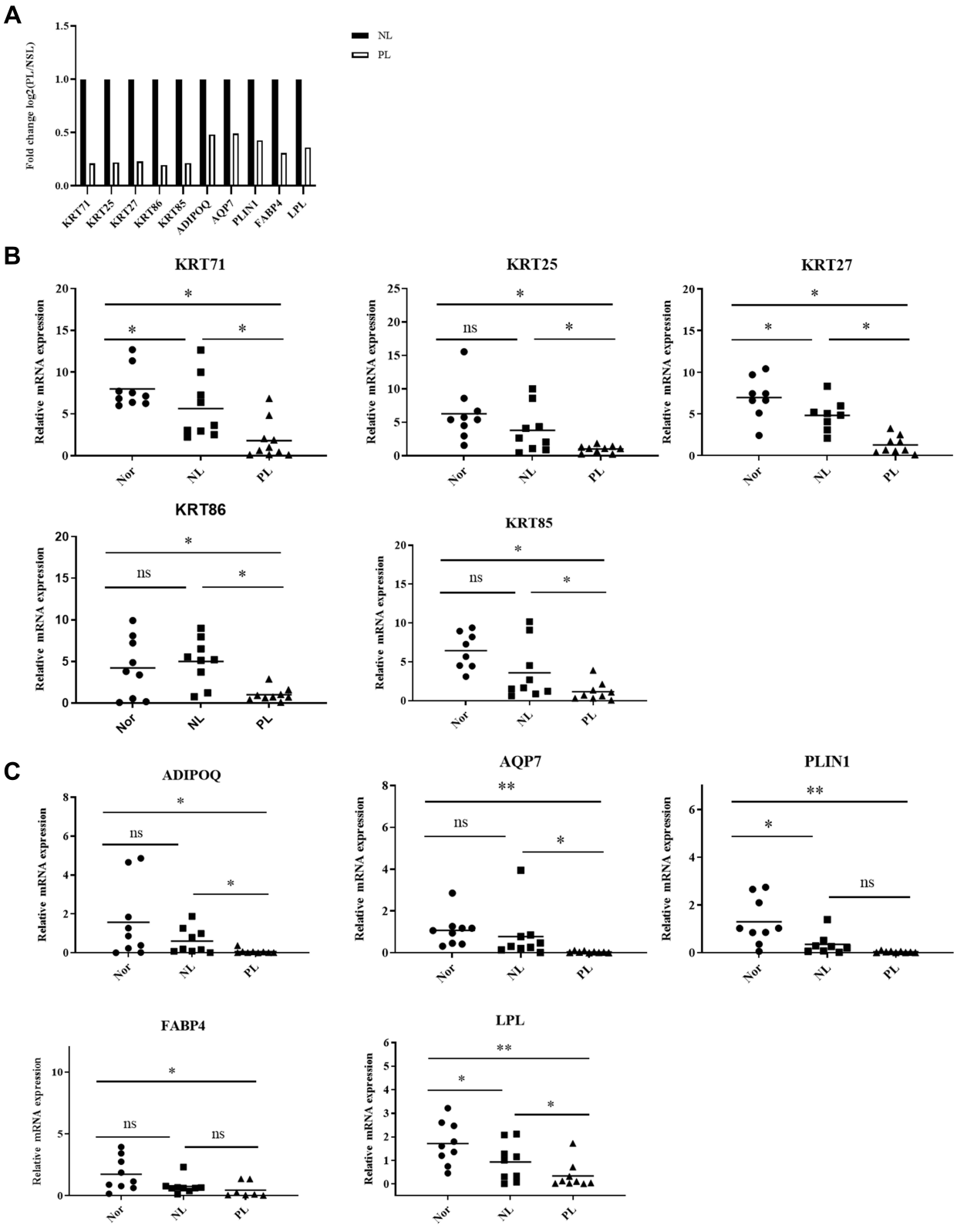

Figure 4 RT-qPCR of target gene expression levels. (**A**) The expression levels of PPAR pathway genes and intermediate filament cytoskeleton genes by RNA-seq. (**B**) The relative expression of PPAR pathway genes were analysis using RT-qPCR. (**C**) The relative expression of intermediate filament cytoskeleton genes were analysis using RT-qPCR. Data are expressed as the mean ± standard deviation. Comparisons between two groups were performed using Student's t-tests. *P<0.05, **P<0.01.
Abbreviations: Nor, Normal tissue; NL, adjacent normal skin; PL, psoriatic lesions.

cascades. Pattern recognition receptors (TLRs, NOD1, NOD2, and CLEC7A) highly expressed during the infection may be one of such cascades.[33] Transcription factors including NF-kBs, JUN-FOS, AHR, GATA3, HIF1A, FOXO1, and FOSL1 can directly inhibit PPARγ expression. All these transcription factors are overstimulated in the inflammatory and immune response. Recently,[34] PPARs and their ligands have been identified in skin, where they control important cellular functions, such as inflammation, proliferation, and differentiation.[35,36] PLIN1 is significantly enriched in the fat metabolism-related PPAR signaling pathway via the DNA demethylation of the PPAR-response elements of the PLIN1 gene promoter upon differentiation. Two other target genes, ADIPOQ and AQP7, were also down-regulated in the psoriasis group compared with the normal control and NL groups.[37] ADIPOQ has been reported to increase AQP3 expression via PPARα-mediated signaling in hepatic stellate cells, while[38] ADIPOQ has been shown to activate PPARα and affect the AMPK pathway,[39] which is involved in the occurrence and development of psoriasis.[40] Furthermore, the PPAR signaling pathway has been suggested as a potential therapeutic target for the treatment of hyperproliferative skin diseases.

Limitations

Our research has several limitations. The number of tested samples was relatively small. More works are needed to verify our findings and illustrate the detailed mechanism of these gene based on larger sample size in the future.

Conclusion

In summary, we screened psoriasis-related mRNA expression profiles by using bioinformatics approaches. The experimentally-validated targets genes of intermediate filament cytoskeleton and PPAR signaling pathway are key regulators of psoriasis lesions. Our results provide a new experimental basis and directions for further research on the effects of mRNA on the occurrence and development of psoriasis.

Ethics Statement

The study was approved by the institutional ethics committee of Taiyuan City Central Hospital (2016005). The study was carried out with the informed consent of the patients themselves and in accordance with the Declaration of Helsinki Principles.

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Disclosure

The authors declare no conflicts of interest for this work.

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