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CXCL10 and its related key genes as potential biomarkers for psoriasis

Evidence from bioinformatics and real-time quantitative polymerase chain reaction

Ailing Zou, MD[a,b], Qichao Jian, MD[a,b,*]

Abstract

Although several studies have attempted to investigate the etiology of and mechanism underlying psoriasis, the precise molecular mechanism remains unclear. Our study aimed to explore the molecular mechanism underlying psoriasis based on bioinformatics.

GSE30999, GSE34248, GSE41662, and GSE50790 datasets were obtained from the Gene Expression Omnibus database. The Gene Expression Omnibus profiles were integrated to obtain differentially expressed genes in R software. Then a series of analyses was performed, such as Gene Ontology annotation, Kyoto Encyclopedia of Genes and Genomes pathway analysis, protein-protein interaction network analysis, among others. The key genes were obtained by CytoHubba, and validated by real-time quantitative polymerase chain reaction.

A total of 359 differentially expressed genes were identified between 270 paired lesional and non-lesional skin groups. The common enriched pathways were nucleotide-binding and oligomerization domain-like receptor signaling pathway, and cytokine-cytokine receptor interaction. Seven key genes were identified, including *CXCL1, ISG15, CXCL10, STAT1, OASL, IFIT1,* and *IFIT3.* These key genes were validated as upregulated in the 4 datasets and M5-induced HaCaT cells.

Our study identified 7 key genes, namely *CXCL1, ISG15, CXCL10, STAT1, OASL, IFIT1,* and *IFIT3*, and 2 mostly enriched pathways (nucleotide-binding and oligomerization domain-like receptor signaling pathway, and cytokine-cytokine receptor interaction) involved in psoriatic pathogenesis. More importantly, *CXCL1, ISG15, STAT1, OASL, IFIT1, IFIT3,* and especially *CXCL10* may be potential biomarkers. Therefore, our findings may bring a new perspective to the molecular mechanism underlying psoriasis and suggest potential biomarkers.

Abbreviations: CXCL = chemokine (C-X-C motif) ligand, DEGs = differentially expressed genes, GEO = Gene Expression Omnibus, GO = Gene Ontology, KEGG = Kyoto Encyclopedia of Genes and Genomes, NOD = nucleotide-binding and oligomerization domain, OASL = oligoadenylate synthetases-like, PPI = protein-protein interaction, RT-qPCR = real-time quantitative polymerase chain reaction.

Keywords: bioinformatics, biomarkers, CXCL10, key genes, psoriasis

1. Introduction

Psoriasis is a chronic and systemic inflammatory cutaneous disorder with a global prevalence of 2% to 3%.[1,2] The occurrence of psoriasis is due to complex interactions among genetics, immunology, and the environment.[1,3] Although many studies have investigated the etiologies and mechanisms, the precise molecular mechanism of psoriasis remains unclear.[3] A thorough exploration of psoriasis pathogenesis would be helpful for discovery of potential biomarkers and could provide novel clues for diagnosis and treatment.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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Bioinformatics has been extensively applied to many diseases, including psoriasis.[4,5] Gene Expression Omnibus (GEO) is an online and free database, that includes various disease gene expression datasets.[4] Thus, we can utilize bioinformatics analysis to conveniently explore the molecular mechanism underlying psoriasis from the GEO database.

In recent years, many scholars have mined key genes related to the pathogenesis of psoriasis by using bioinformatics methods.[5–7] For example, Gao et al[7] reported 7 key genes in psoriasis (*HERC6, MX1, OAS2, OASL, OAS3, ISG15,* and *RSAD2*). Meanwhile, Delic et al[5] considered *AURKA, CSK2, CDC45, CENPE, DLGP5, HMMR, IFIT1, IFI6, IFI27, ISG20, NDC80, NUF2, MCM10, RRM2, SPC25, RSAD2,* and *TTK* as key genes. These conclusions demonstrate that numerous genes are related to the pathogenesis of psoriasis. Thus, we can still explore other key genes from different viewpoints.

As we know, the diagnosis of psoriasis is not difficult, however its effective treatment does not exist till now.[8] It is helpful to explore key genes for discovering potential biomarkers and provide therapeutic targets for psoriasis. Thus, our primary objective is to search key genes for psoriasis that could be potential biomarkers.

In our study, we attempted to identify key genes and associated pathways in psoriasis using bioinformatics analysis, and compare the expression levels of key genes between lesional and non-lesional psoriatic skin based on 4 datasets. Finally, we carried out real-time quantitative polymerase chain reaction (RT-qPCR) experiments in M5 induced HaCaT cells for validation. Since some studies confirmed that M5 (IL-22, TNF-a, IL-17A, IL-1a, and Oncostatin M) can induce a better psoriatic cell model,[9–14] we use it to treat HaCaT cells in our experiments. Therefore, our findings may bring a new perspective to the molecular mechanism underlying psoriasis and suggest potential biomarkers.

2. Materials and Methods

2.1. Microarray datasets collection and identification of differentially expressed genes

Figure 1 demonstrates the workflow of this study. Four microarray datasets (GSE30999,[15] GSE34248,[16] GSE41662,[16] and GSE50790[17]) were downloaded from GEO (https://www.ncbi.nlm.nih.gov/geo/). A total of 127 paired lesional and non-lesional skin samples were selected as subjects from plaque psoriasis patients in the 4 datasets. All subjects were from homo sapiens and GPL570 platform ([HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array). The detailed sample information was summarized in Table 1 (The data were by the year of March 2021).

The raw data of 4 datasets were collated and analyzed using R software (version4.0.2.). Since the raw data were from 4 different microarray datasets, the collated data were processed by background correction and normalized using the "affy" package,[18] and the batch effect was eliminated using the ComBat function of sva package.[19] The limma package was used to identify differentially expressed genes (DEGs) between 127 paired lesional and non-lesional psoriatic skin tissues. The cutoff value was set as $|\log FC| > 1.5$ and adjusted $P < .05$, which was demonstrated as a volcano plot. Then the clustering of samples was shown as a heatmap.

2.2. Gene Ontology and Kyoto Encyclopedia of Genes and Genomes enrichment analyses of DEGs

Gene Ontology (GO) annotation and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis of DEGs were performed using Metascape (http://metascape.org), which is a free and online analysis tool.[20] GO annotation comprises cellular component, molecular function, and biological process.

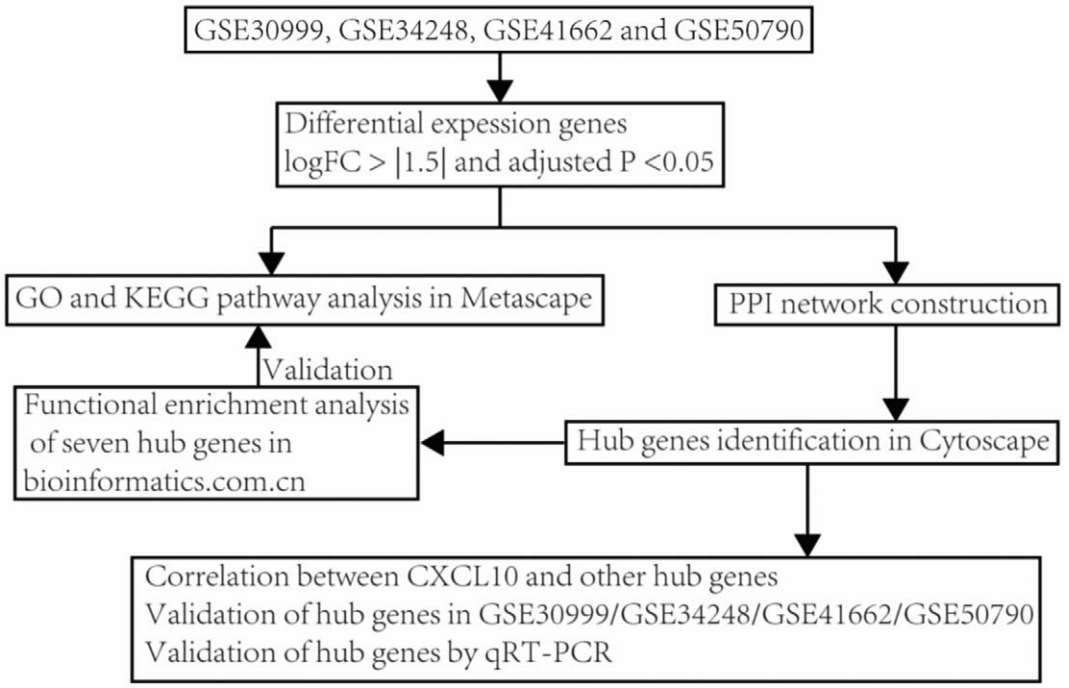

Figure 1. The workflow of this study. GO = Gene Ontology, KEGG = Kyoto Encyclopedia of Genes and Genomes, PPI = protein-protein interaction, RT-qPCR = real-time quantitative polymerase chain reaction.

Table 1

Information of 4 datasets.

GEO accession	GSE30999	GSE34248	GSE41662	GSE50790
Organism	Homo sapiens	Homo sapiens	Homo sapiens	Homo sapiens
Tissue	Skin	Skin	Skin	Skin
Platform	GPL570	GPL570	GPL570	GPL570
Sample	Paired LS/NL	Paired LS/NL	Paired LS/NL	Paired LS/NL
Pair no.	85	14	24	4
Type	Plaque psoriasis	Plaque psoriasis	Plaque psoriasis	Plaque psoriasis
Citation	Suárez-Fariñas et al[15]	Bigler et al[16]	Bigler et al[16]	Swindell et al[17]

GEO = Gene Expression Omnibus, LS = lesional skin, NL = non-lesional skin.

The cutoff criteria were a P value $< .05$, minimum overlap of 3, and minimum enrichment of 1.5.

2.3. Protein-protein interaction network construction and screening for key genes

The STRING database (version 11.0, http://www.string-db.org/) was utilized to obtain protein-protein interaction (PPI) information for DEGs (high confidence of 0.7 was chosen).[21] Then, Cytoscape 3.8.0 was applied to visualize the PPI network.[22] The modules of the PPI network were explored using MCODE, and key genes were screened with CytoHubba. This could provide 12 topological analysis methods to identify the top 10 genes. A key gene was identified, if the gene was predicted to be one of the top 10 genes in all 12 methods. Finally, the interactions between the hub genes were returned to the STRING database for analysis.

2.4. Functional enrichment analysis of 7 key genes

To confirm the validity of the 7 key genes, functional enrichment analysis of these genes was further analyzed with http://www.bioinformatics.com.cn.

2.5. Validation of 7 key genes in the 4 datasets

The 7 key genes were validated in the 4 aforementioned datasets. Moreover, the relationships between *CXCL10* and the other hub genes were also confirmed based on the 4 datasets.

2.6. Validation of 7 key genes via RT-qPCR

First, HaCaT cells (Shanghai iCell Bioscience Inc.) were cultured in Dulbecco Modified Eagle's Medium at 37°C in a 5% CO_2 environment with 10% fetal bovine serum and 1% penicillin and streptomycin. Then, the cells were treated with 10 ng/mLM5 (IL-22, TNF-a, IL-17A, IL-1a, and Oncostatin M) (PeproTech) for 48 hours to induce the psoriasis cell model.

After that, total RNA was extracted from M5-treated HaCaT cells using the TRIpure Total RNA Extraction Reagent (#EP013, ELK Biotechnology, China). Total RNA was reverse transcribed using the EntiLink 1st Strand Cdna Synthesis Kit (#EQ003, ELK Biotechnology, China) according to the manufacturer's protocols. The expression levels of the 7 key genes in HaCaT cells and M5-treated HaCaT cells were detected by RT-qPCR using EnTurbo SYBR Green PCR SuperMix (#EQ001, ELK Biotech-

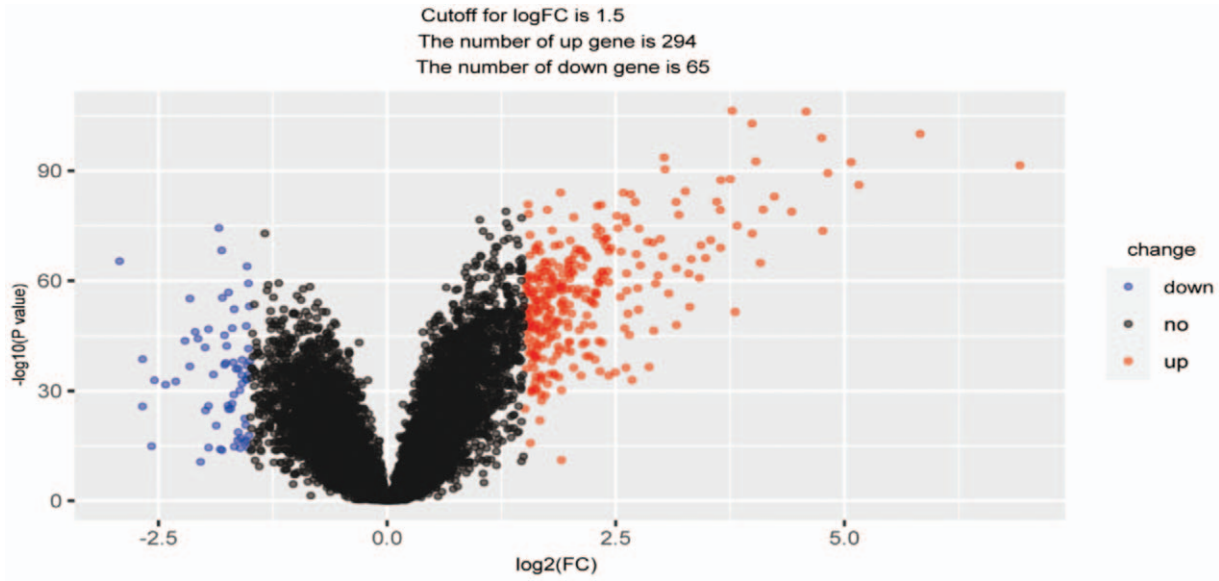

Figure 2. The volcano plot of differentially expressed genes (DEGs). Red, black, and green dots indicate up-regulated, no significant and down-regulated genes, respectively. A total of 359 DEGs were identified basing on |log2 FC| > 1.5 and adjusted $P < .05$.

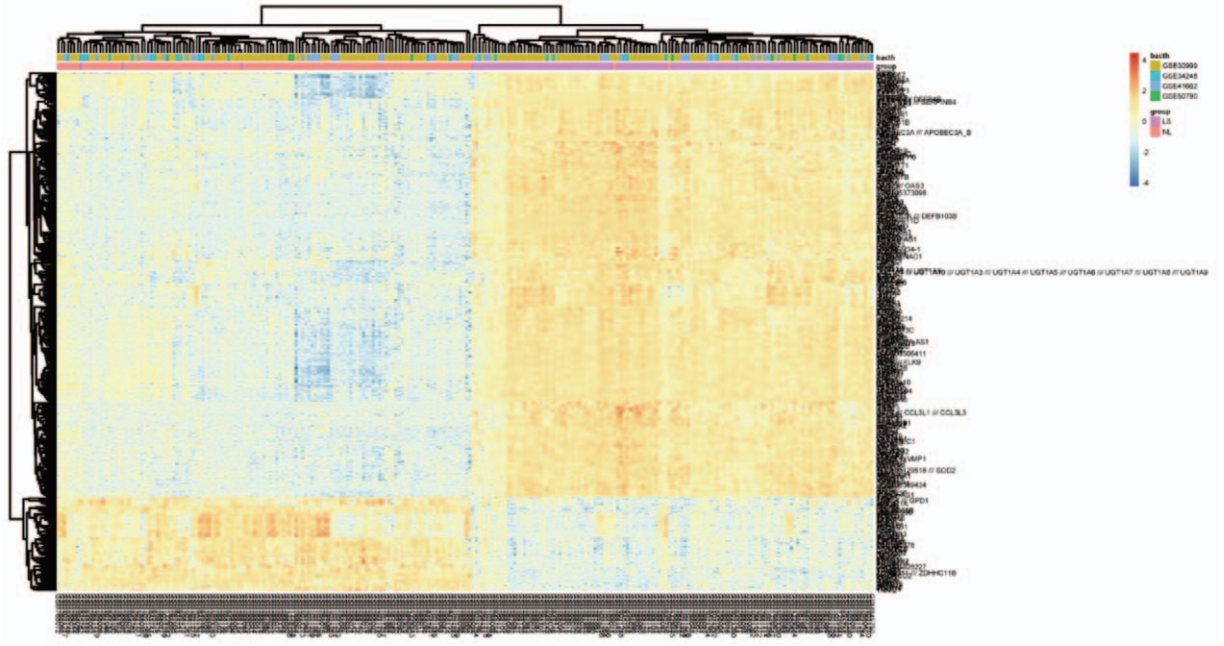

Figure 3. The heatmap of DEGs. The orange and blue colors represent up-regulated and down-regulated genes, respectively. DEGs = differentially expressed genes.

nology, China) with the StepOne Real-Time PCR System (Life Technologies). The primer sequences were shown in Table S1, Supplemental Digital Content, http://links.lww.com/MD/G412.

2.7. Statistical analysis

The data extracted from GEO datasets were examined by the normality test and homogeneity of variance test. *t* testing and analysis of variance testing were used for comparisons between 2 groups and among 3 or more groups respectively. Spearman correlation analysis was utilized to investigate the relationships between *CXCL10* and other hub genes. GraphPad Prism 8.0.1 was used to perform these tests.

3. Results

3.1. Identification of DEGs

Finally, 359 DEGs were identified between 270 paired lesional and non-lesional skin groups with $|\log FC| > 1.5$ and adjusted $P < .05$, of which 284 were up-regulated and 65 were down-regulated. The volcano plot and heatmap of DEGs were shown in Figures 2 and 3, respectively.

3.2. GO and KEGG pathway analyses of DEGs

The GO annotation of DEGs was mostly enriched in 6 clustering groups, including response to bacterium, defense response to other organism, anti-microbial humoral response, flavonoid glucuronidation, skin development, and monocarboxylic acid metabolic process (Fig. 4A, B). The top 20 GO items were of the biological process group (15), and molecular function group (5) (Table 2). KEGG pathway analysis of DEGs indicated that genes were mostly enriched in 3 clustering groups, including steroid hormone biosynthesis, nucleotide-binding and oligomerization domain (NOD)-like receptor signaling pathway, and cytokine-cytokine receptor interaction (Fig. 4C, D). The top 20 KEGG pathway enriched items were shown in Table 3.

3.3. PPI network construction and screening for key genes

The PPI network of 359 DEGs was acquired with the STRING database, which was visualized using Cytoscape software (Fig. 5A). Then MCODE was used to identify functional modules. There were 6 modules, of which cluster 1 consisted of 28 nodes and 196 edges (Fig. 5B), including *GAL*, *CXCL13*, *GBP1*, *IFIT3*, *RTP4*, *IFIT1*, *MX1*, *OASL*, *IFI44*, *ISG15*, *CCL27*, *OAS1*, *RSAD2*, *CXCR2*, *CXCL8*, *IFI44L*, *IRF7*, *STAT1*, *CXCL1*, *PTGER3*, *OAS2*, *HERC6*, *IFI6*, *IFI27*, *CCL20*, *CXCL9*, *CXCL10*, and *CXCL2* (Table 4). Seven genes, namely *CXCL1*, *ISG15*, *CXCL10*, *STAT1*, *OASL*, *IFIT1*, and *IFIT3*, were considered the key genes by CytoHubba (Table 5). Subsequently, the relationships among the 7 key genes were explored with the STRING database and *CXCL10* was central for the connection (Fig. 5C).

3.4. Functional enrichment analysis of 7 key genes

Seven key genes were further analyzed using an online tool (http://www.bioinformatics.com.cn). The enrichment results of 7 hub genes were shown in chord plots based on the adjusted *P* values (Fig. 6). For GO analysis, the top 5 terms were response to bacterium, defense response to other organism, anti-microbial humoral response, flavonoid glucuronidation, and chemokine receptor binding (Fig. 6A). For KEGG pathway analysis, the top 3 terms were NOD-like receptor signaling pathway, cytokine-cytokine receptor interaction, and amoebiasis (Fig. 6B). These results were consistent with the Metascape analysis, which strengthened the reliability of the results.

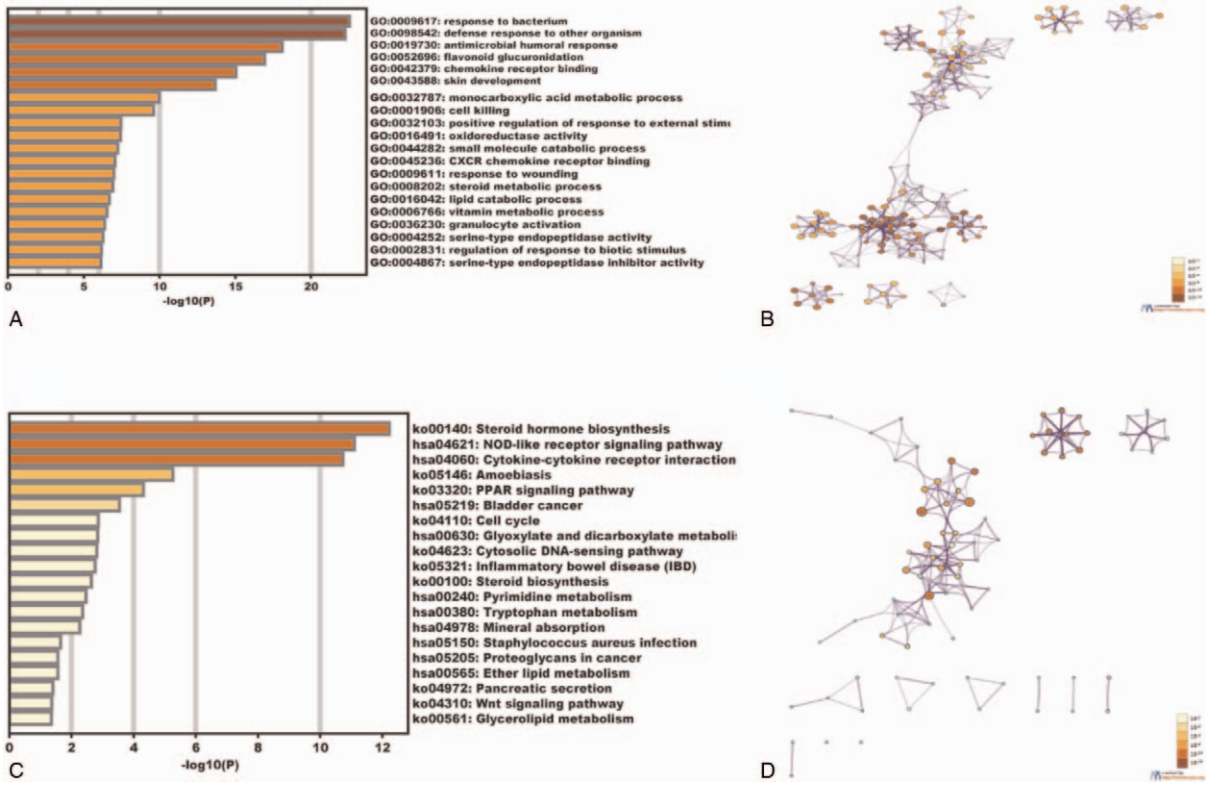

Figure 4. The GO and KEGG pathway analyses of DEGs in Metascape. (A) Heatmap of GO enriched terms colored by *P* values. (B) Network of GO enriched terms colored by *P* value. (C) Heatmap of KEGG enriched terms colored by *P* values. (D) Network of KEGG enriched terms colored by *P* value. DEGs = differentially expressed genes, GO = Gene Ontology, KEGG = Kyoto Encyclopedia of Genes and Genomes.

3.5. Validation of 7 key genes in 4 datasets

The expression levels of 7 key genes were confirmed in GSE30999, GSE34248, GSE41662, and GSE50790 datasets. Except for *CXCL1*, *STAT1*, and *OASL* in GSE50790, the other key genes were obviously up-regulated in psoriatic lesional skin tissues (Fig. 7).

Table 2

The top 20 GO items of DEGs.

GO	Category	Description	Count	%	Log10(P)	Log10(q)
GO:0009617	BP	Response to bacterium	53	14.25	−22.54	−18.21
GO:0098542	BP	Defense response to other organism	48	12.9	−22.25	−18.21
GO:0019730	BP	Anti-microbial humoral response	23	6.18	−18.1	−14.22
GO:0052696	BP	Flavonoid glucuronidation	9	2.42	−16.93	−13.18
GO:0043588	BP	Skin development	31	8.33	−13.69	−10.48
GO:0032787	BP	Monocarboxylic acid metabolic process	33	8.87	−9.98	−7.24
GO:0001906	BP	Cell killing	17	4.57	−9.62	−6.91
GO:0032103	BP	Positive regulation of response to external stimulus	20	5.38	−7.45	−5.01
GO:0044282	BP	Small molecule catabolic process	23	6.18	−7.24	−4.82
GO:0009611	BP	Response to wounding	29	7.8	−6.99	−4.58
GO:0008202	BP	Steroid metabolic process	19	5.11	−6.9	−4.51
GO:0016042	BP	Lipid catabolic process	19	5.11	−6.69	−4.3
GO:0006766	BP	Vitamin metabolic process	12	3.23	−6.53	−4.16
GO:0036230	BP	Granulocyte activation	23	6.18	−6.38	−4.02
GO:0002831	BP	Regulation of response to biotic stimulus	12	3.23	−6.17	−3.82
GO:0042379	MF	Chemokine receptor binding	16	4.3	−15.05	−11.66
GO:0016491	MF	Oxidoreductase activity	31	8.33	−7.43	−5
GO:0045236	MF	CXCR chemokine receptor binding	6	1.61	−7.07	−4.65
GO:0004252	MF	Serine-type endopeptidase activity	13	3.49	−6.27	−3.92
GO:0004867	MF	Serine-type endopeptidase inhibitor activity	10	2.69	−6.12	−3.79

BP = biological process, DEGs = differentially expressed genes, GO = Gene Ontology, MF = molecular function.

Table 3

The top 20 KEGG pathways of DEGs.

GO	Category	Description	Count	%	Log10(P)	Log10(q)
ko00140	KEGG pathway	Steroid hormone biosynthesis	13	3.49	−12.22	−9.75
hsa04621	KEGG pathway	NOD-like receptor signaling pathway	19	5.11	−11.11	−8.9
hsa04060	KEGG pathway	Cytokine-cytokine receptor interaction	24	6.45	−10.74	−8.68
ko05146	KEGG pathway	Amoebiasis	9	2.42	−5.26	−3.91
ko03320	KEGG pathway	PPAR signaling pathway	7	1.88	−4.31	−3.01
hsa05219	KEGG pathway	Bladder cancer	5	1.34	−3.54	−2.29
ko04110	KEGG pathway	Cell cycle	7	1.88	−2.86	−1.65
hsa00630	KEGG pathway	Glyoxylate and dicarboxylate metabolism	4	1.08	−2.84	−1.65
ko04623	KEGG pathway	Cytosolic DNA-sensing pathway	5	1.34	−2.82	−1.64
ko05321	KEGG pathway	Inflammatory bowel disease (IBD)	5	1.34	−2.76	−1.59
ko00100	KEGG pathway	Steroid biosynthesis	3	0.81	−2.65	−1.51
hsa00240	KEGG pathway	Pyrimidine metabolism	6	1.61	−2.47	−1.37
hsa00380	KEGG pathway	Tryptophan metabolism	4	1.08	−2.36	−1.28
hsa04978	KEGG pathway	Mineral absorption	4	1.08	−2.27	−1.2
hsa05150	KEGG pathway	Staphylococcus aureus infection	4	1.08	−1.66	−0.68
hsa05205	KEGG pathway	Proteoglycans in cancer	7	1.88	−1.57	−0.61
hsa00565	KEGG pathway	Ether lipid metabolism	3	0.81	−1.56	−0.61
ko04972	KEGG pathway	Pancreatic secretion	4	1.08	−1.41	−0.48
ko04310	KEGG pathway	Wnt signaling pathway	5	1.34	−1.37	−0.45
ko00561	KEGG pathway	Glycerolipid metabolism	3	0.81	−1.36	−0.44

DEGs = differentially expressed genes, GO = Gene Ontology, KEGG = Kyoto Encyclopedia of Genes and Genomes, NOD = nucleotide-binding and oligomerization domain.

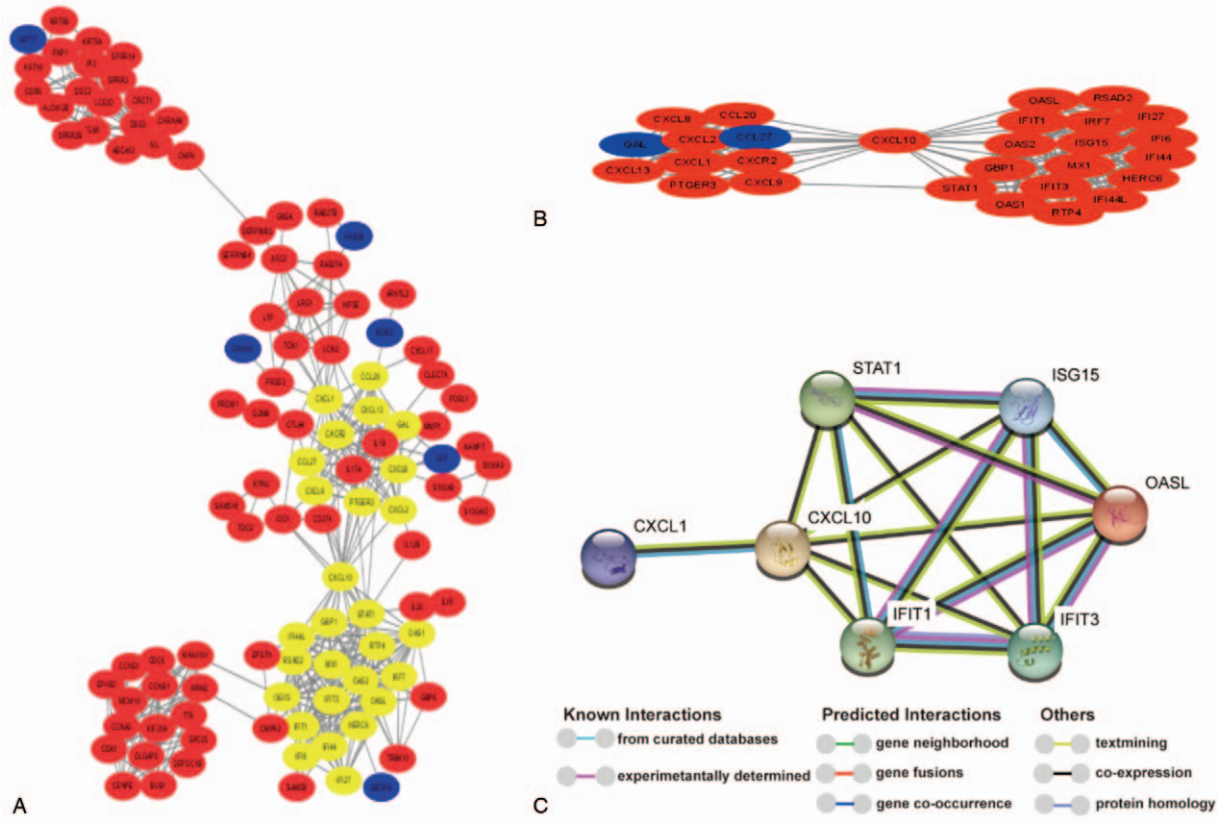

Figure 5. PPI network and hub genes. (A) The PPI network was constructed in Cytoscape, with upregulated genes revealed in red ellipses, downregulated genes in blue ellipses, and cluster 1 genes in yellow ellipses. (B) Cluster 1 network was constructed with upregulated genes revealed in red ellipses and downregulated genes in blue ellipses. (C) The connection function between 7 hub genes in STRING database. PPI = protein-protein interaction.

Table 4

The detailed information of cluster networks in MCODE.

Cluster	Score (density*#nodes)	Nodes	Edges	Node IDs
1	14.519	28	196	GAL, CXCL13, GBP1, IFIT3, RTP4, IFIT1, MX1, OASL, IFI44, ISG15, CCL27, OAS1, RSAD2, CXCR2, CXCL8, IFI44L, IRF7, STAT1, CXCL1, PTGER3, OAS2, HERC6, IFI6, IFI27, CCL20, CXCL9, CXCL10, CXCL2
2	12.167	13	73	DLGAP5, KIAA0101, KIF20A, CCNA2, CDC6, BUB1, CENPE, RRM2, CDK1, CCNB1, MCM10, TTK, SPC25
3	9.8	11	49	LCE3D, SPRR2B, IVL, SPRR3, SPRR1A, PKP1, DSG3, CDSN, DSC2, TGM1, PI3
4	6	9	24	TCN1, IL1B, IL17A, RAB27A, LRG1, HPSE, ARG1, LCN2, LTF
5	4	4	6	KRT16, KRT6A, KRT77, KRT6B
6	3	3	3	S100A12, S100A9, S100A8

Table 5

The detailed information of 7 key genes.

Rank	Gene symbol	Change	LogFC	Adj. *P* value	Occurrences in 12 statistical methods by CytoHubba	Full name (human)
1	CXCL1	Up	3.4145	9.27E-42	8	C-X-C motif chemokine ligand 1
1	ISG15	Up	1.9624	2.62E-38	8	ISG15 ubiquitin like modifier
2	CXCL10	Up	2.3289	2.19E-27	7	C-X-C motif chemokine ligand 10
3	STAT1	Up	1.7999	1.36E-47	6	Signal transducer and activator of transcription 1
4	OASL	Up	3.7520	1.47E-66	5	2′-5′-oligoadenylate synthetase like
4	IFIT1	Up	1.7003	3.18E-33	5	Interferon induced protein with tetratricopeptide repeats 1
4	IFIT3	Up	1.6149	4.02E-34	5	Interferon induced protein with tetratricopeptide repeats 3

3.6. Relationship between CXCL10 and the other key genes

For the relationships among the 7 key genes, *CXCL10* was central to the network (Fig. 5C), had a higher rank (Table 5), and a demonstrated positive correlation with the other 6 key genes in the 4 aforementioned datasets (Fig. 8), suggesting the close relationship between *CXCL10* and the other 6 key genes.

3.7. Validation of key genes via qRT-PCR

The expression levels of 7 key genes were validated by RT-qPCR (n = 3). The results of qRT-PCR showed that the transcription levels of *CXCL10*, *CXCL1*, *ISG15*, *STAT1*, *OASL*, *IFIT1*, and *ITIT3* were significantly up-regulated in 10 ng/mL M5 induced HaCaT cells (Fig. 9). The expression levels of these genes were consistent with the microarray results.

4. Discussion

Psoriasis is a chronic, relapsing-remitting, and inflammatory skin disease that affects 2% to 3% of the population worldwide.[1] Recurrence has been common after treatment in psoriasis. That is to say, there are currently no known radical treatments for

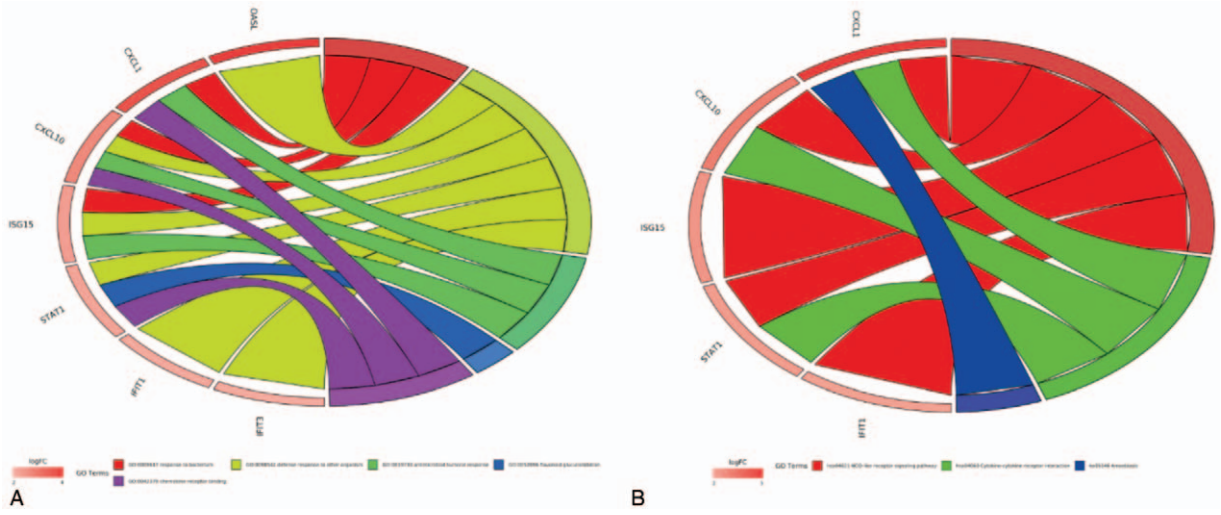

Figure 6. The chord plots of enrichment analysis of 7 hub genes. (A) GO enrichment analysis. (B) KEGG enrichment analysis. GO = Gene Ontology, KEGG = Kyoto Encyclopedia of Genes and Genomes.

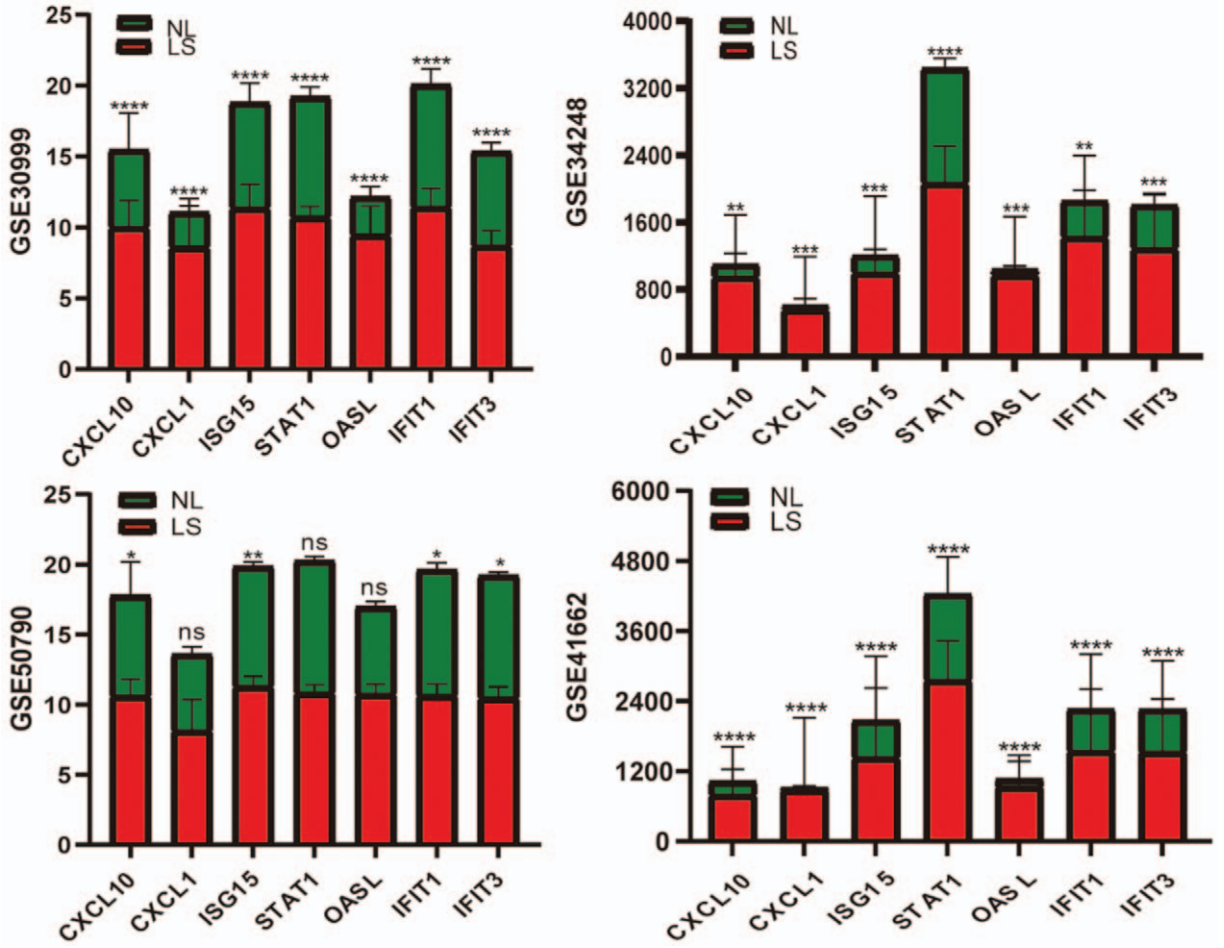

Figure 7. The expression of 7 hub genes in 4 datasets. The green bar indicates non-lesional skin groups, and the red bar indicates lesional skin groups. Paired *t* testing was performed to compare the means of 2 groups. $^{*}P<.05$; $^{**}P<.01$; $^{***}P<.001$; $^{****}P<.0001$. LS = lesional skin, NL = non-lesional skin, ns = no significance.

psoriasis.[2] Thus, it is important and urgent to investigate the molecular mechanisms involved in the pathogenesis of psoriasis to provide new clues for treatment. An important discovery of our study was the confirmation of key genes in psoriasis by bioinformatics and via RT-qPCR. The 7 key genes comprised *CXCL10, CXCL1, ISG15, STAT1, OASL, IFIT1,* and *IFIT3*, and the 2 common enriched pathways were NOD-like receptor signaling pathway and cytokine-cytokine receptor interaction.

Among the 7 key genes, *CXCL10* was a higher ranked gene and had positive correlations with other 6 hub genes, suggesting that it might be the most significant gene. Furthermore, the RT-qPCR results of *CXCL10* confirmed this prediction. Some studies have also reported several hub genes in psoriasis, some of which are consistent with ours,[6,7,23] especially the study of Luo et al. They reported that *CXCR2, CXCL10, IVL, OASL,* and *ISG15* were hub genes, and *CXCL10* was the hub gene with the highest degree.[23] However they did not perform experiments to validate the hub genes. *CXCL10* is a member of the CXC family of chemokines, and plays a significant role in inflammation through its T-cell chemotactic and adhesion properties.[24] Researches have also indicated *CXCL10* is up-regulated in psoriatic skin lesions and serum.[24,25] It has been hypothesized that *CXCL10* could be a good marker for psoriasis.[26] Although *CXCL10* and *CXCL1* belong to the chemokine "CXC" family,[27] they play different roles in psoriasis. *CXCL10* attracts T helper (Th) 1 cells, and whereas *CXCL1* attracts neutrophils.[28] It was reported that *CXCL10* production by keratinocytes depends on STAT1.[29] *STAT1* is known as a member of the STAT family, involved in type I and type II interferon signaling.[30] The expression of *STAT1* is increased in psoriatic skin, and it also has a vital role in the pathogenesis of psoriasis.[31]

The remaining 4 genes (*ISG15, OASL, IFIT1,* and *IFIT3*) are anti-viral genes, which may explain the relatively fewer viral skin infections found in psoriasis patients. Ubiquitin-like protein ISG15 is an interferon-stimulated protein that has a critical role in the control of microbial infections.[32,33] Some studies reported that ISG15 is elevated in psoriatic skin compared with levels in atopic dermatitis skin and healthy skin.[34] The interferon-inducible oligoadenylate synthetases-like (OASL) protein belongs to the atypical oligoadenylate synthetase family, possesses anti-viral activity, and boosts innate immunity.[35,36] Gao et al[7] also identified *OASL* as a hub gene, but it has been rarely studied in psoriasis patients. Although the expression of *OASL* was up-regulated in M5-induced HaCaT cells in our study, this needs to be further confirmed.

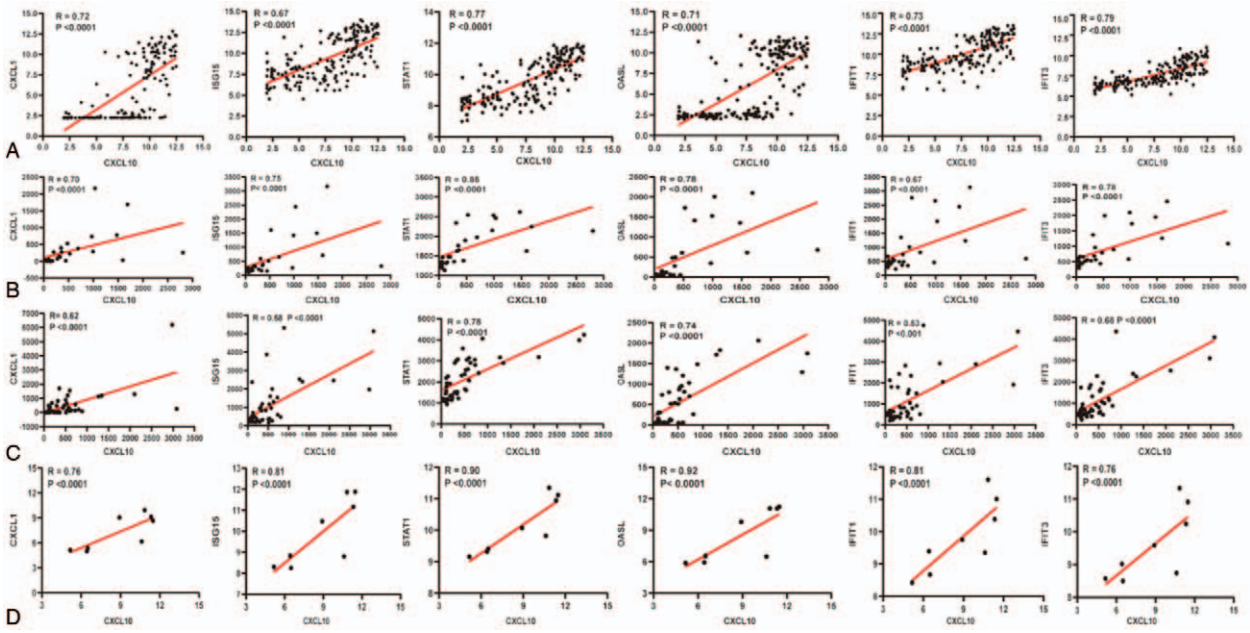

Figure 8. Spearman correlation analysis confirming the significant correlation between CXCL10 and the other hub genes. (A) GSE30999: CXCL1 (R = 0.72), ISG15 (R = 0.67), STAT1 (R = 0.77), OASL (R = 0.71), IFIT1 (R = 0.73), IFIT3 (R = 0.79). (B) GSE34248: CXCL1 (R = 0.70), ISG15 (R = 0.75), STAT1 (R = 0.85), OASL (R = 0.78), IFIT1 (R = 0.67), IFIT3 (R = 0.78). (C) GSE41662: CXCL1 (R = 0.62), ISG15 (R = 0.58), STAT1 (R = 0.78), OASL (R = 0.74), IFIT1 (R = 0.53), IFIT3 (R = 0.68). (D) GSE50790: CXCL1 (R = 0.76), ISG15 (R = 0.81), STAT1 (R = 0.90), OASL (R = 0.92), IFIT1 (R = 0.81), IFIT3 (R = 0.76).

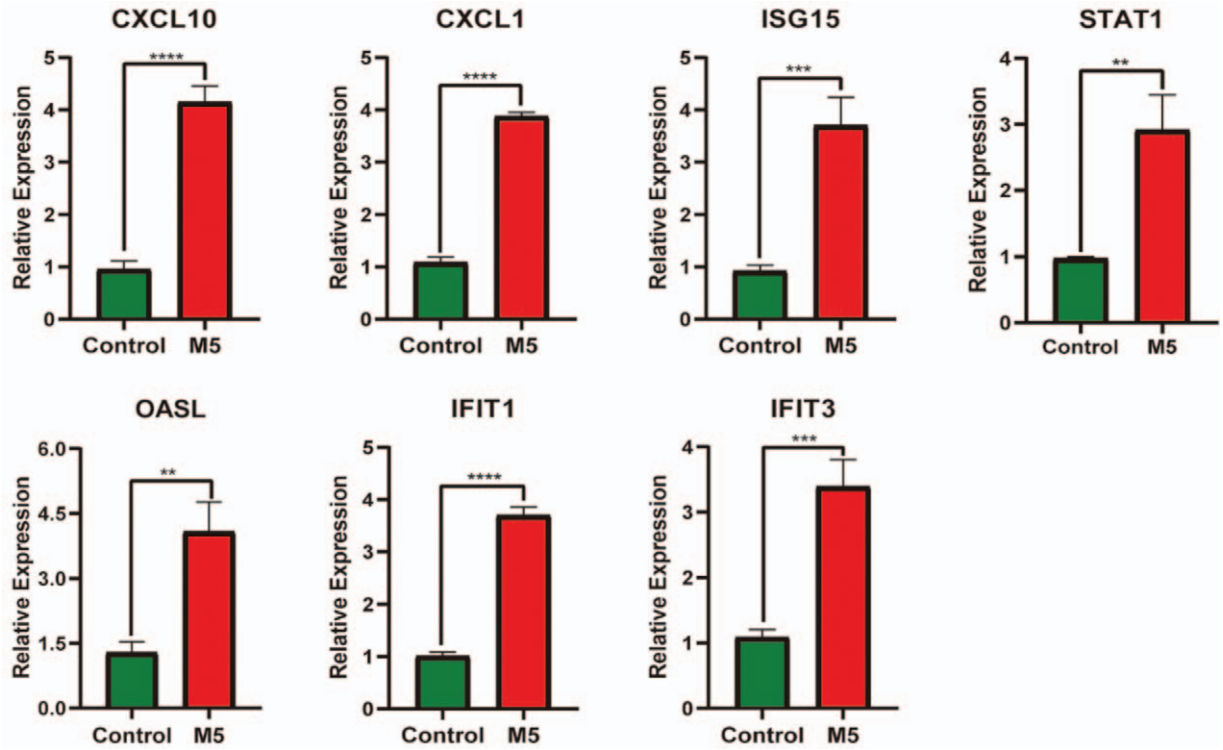

Figure 9. The results of RT-qPCR. The transcription levels of CXCL10, CXCL1, ISG15, STAT1, OASL, IFIT1, and ITIT3 were significantly up-regulated in M5 group. *t* testing was performed to compare the means of 2 groups. $^{**}P < .01$; $^{***}P < .001$; $^{****}P < .0001$. M5, HaCat cells were treated with 10 ng/mL M5 (IL-1a, IL-17, IL-22, TNF-α, and Oncostatin M); Control, HaCat cells without M5 stimulation. RT-qPCR = real-time quantitative polymerase chain reaction.

The IFITs include *IFIT1, IFIT2, IFIT3,* and *IFIT5*,[37] which regulate immune responses and function as essential anti-viral proteins.[38] One study indicated that *IFIT3* binding to *IFIT1* is vital for stabilizing *IFIT1* expression, and is indispensable for inhibiting infection by viruses lacking 2′-O methylation.[38] In this study, *IFIT1* was enriched in the NOD-like receptor signaling pathway, but *IFIT3* was not. Currently, there are few studies on IFITs in psoriasis; however, *IFIT1* and *IFIT3* are overexpressed in oral squamous cell carcinoma, and promote tumor growth and regional and distant metastasis.[37] Therefore, this new finding warrants further study.

The NOD-like receptor is a type of pattern-recognition receptor. It is also associated with various diseases related to infection and immunity.[39] Some studies showed that the NOD-like receptor signaling pathway was enriched in psoriatic epidermis.[40] Meanwhile, some researchers have found that cytokine-cytokine receptor interaction is related to the pathogenesis of psoriasis via combined transcriptomic analysis.[41] These results are consistent with ours.

In summary, we identified 7 key genes and 2 mostly enriched pathways for psoriasis. Our findings may bring a profound understanding for the molecular mechanism underlying psoriasis. However, this study has some limitations. First, the sample size is limited to a portion of the publicly available datasets and cannot be representative of the entire population. Second, there is potential bias of our data, due to different datasets. Third, we only performed 1 cell experiment. More experiments, such as skin tissues, are needed to support our results.

5. Conclusion

In our study, we tried to identify DEGs between psoriatic and non-psoriatic lesions by bioinformatics, discovered 7 hub genes and 2 mostly enriched pathways that might participate in the pathogenesis of psoriasis, and validated the hub genes upregulated in a psoriatic cell model through RT-qPCR. More interestingly, the 7 hub genes, namely *CXCL1, ISG15, STAT1, OASL, IFIT1, IFIT3,* and especially *CXCL10* may be used as potential biomarkers. Therefore, our findings may bring a new perspective to the molecular mechanism underlying psoriasis and suggest potential biomarkers.

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Author contributions

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