Integrated Bioinformatic Analysis of Key Biomarkers and Signaling Pathways in Psoriasis

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Research

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Abstract

Background: Psoriasis is a relatively common autoimmune inflammatory skin disease with a chronic etiology. The present study was designed to detect novel biomarkers and pathways associated with psoriasis incidence.

Methods: Differentially expressed genes (DEGs) associated with psoriasis in the Gene Expression Omnibus (GEO) database were identified, and their functional roles and interactions were then annotated and evaluated through GO, KEGG, and gene set variation (GSVA) analyses. In addition, the STRING database was leveraged to construct a protein-protein interaction (PPI) network, and key hub genes from this network were validated as being relevant through receiver operating characteristic (ROC) curve analyses of three additional GEO datasets. The CIBERSORT database was additionally used to assess the relationship between these gene expression-related findings and immune cell infiltration.

Results: In total 197 psoriasis-related DEGs were identified and found to primarily be associated with the NOD-like receptor, IL-17, and cytokine-cytokine receptor interaction signaling pathways. GSVA revealed significant differences between normal and lesional groups ($P < 0.05$), while PPI network analyses identified CXCL10 as the hub gene with the highest degree value, whereas IRF7, IFIT3, OAS1, GBP1, and ISG15 were promising candidate genes for the therapeutic treatment of psoriasis. ROC analyses confirmed that these 6 hub genes exhibited good diagnostic efficacy ($AUC > 70\%$), and were predicted to be associated with increased sensitivity to 10 drugs ($P < 0.01$). The CIBERSORT database further predicted that these hub genes were associated with infiltration by 22 different immune cell types.

Conclusion: These results offer a robust foundation for future studies of the molecular basis for psoriasis, potentially guiding efforts to treat this common and disruptive disease.

Introduction

Psoriasis is a chronic autoimmune-mediated inflammatory skin condition that arises as a consequence of both environmental and genetic factors, leading affected patients to suffer from scaly erythema [1]. An estimated 2% of people in Europe and 0.47% of people in China are thought to suffer from psoriasis [2], and many of these patients suffer from poor quality of life [3]. While psoriasis is not a life-threatening condition, it can impose significant psychological and financial burdens on affected individuals. A number of therapies that can effectively treat psoriasis have been developed in recent years [4–5], including systemic retinoic acid delivery, immunosuppressant or cyclosporine treatment, and external glucocorticoid or retinoic acid application. However, some patients experience significant adverse reactions to these treatments. Owing to its complex and multifactorial etiology, psoriasis remains impossible to cure. It is thus vital that the molecular mechanism governing psoriasis development be clarified in order to guide more effective patient treatment.

Psoriasis exhibits polygenic patterns of inheritance and is primarily driven by T cells, with a range of factors stimulating excessive autoimmune activity in affected individuals. Recent studies of the

immunological basis for psoriasis have led to the development and commercialization of novel biological therapeutics targeting TNF- α , PDE-4, T cells, small cell signal transduction molecules, and VEGF. These inhibitors exhibit excellent clinical efficacy, but they are extremely expensive and have the potential to increase the risk of certain infections in treated patients, making them imperfect therapeutic agents.

Several different chemokine signaling pathways have been linked to the incidence of psoriasis [6–7]. These include several CXC family chemokines that can facilitate inflammatory T cell responses (CXCL10, CXCL16) and neutrophil responses (CXCL1, CXCL5) in psoriatic contexts, with these factors signaling through receptors including CXCR1 and CXCR2 in T cells, and CXCR3 and CXCR6 in neutrophils [8]. Keratinocytes and other cells in the dermis of plaque psoriasis patients express CXCL10 and its receptor CXCR3, and CXCL10 levels in patient serum fall following patient treatment. While patients with newly diagnosed early-stage psoriasis often exhibit high CXCL10 levels, these levels tend to be lower in the serum of patients who have been suffering from this disease for longer periods of time [9]. Antibodies targeting CCL2 and CXCL10 can suppress the expression of these chemokines in psoriatic lesions, thereby reducing the severity of psoriasis as measured using PASI scores [10]. More research, however, is needed to fully understand the role of CXCL10 in psoriasis patients.

In recent decades, a range of microarray and sequencing technologies have been used to detect genetic and transcriptomic changes associated with particular disease states. These analyses have supported the identification of differentially expressed genes (DEGs) and functional pathways associated with the development and progression of psoriasis. However, individual microarray analyses have the potential to yield false-positive results that cannot be replicated. In addition, microarrays conducted using different platforms may exhibit result discordance owing to small sample sizes and to differences in the underlying platforms and statistical methods employed in individual studies. As such, further comprehensive analyses are necessary to ensure the reliable identification of robust diagnostic biomarkers and therapeutic targets capable of aiding in the treatment of psoriasis.

The present study was therefore designed to conduct an integrated analysis of three microarray datasets from the Gene Expression Omnibus (GEO) so as to identify key genes that were differentially expressed when comparing normal and psoriatic skin samples. Additional enrichment and network analyses were then performed to clarify the relationships between these DEGs and the progression of psoriasis. Together, our data provide a comprehensive framework that highlights the molecular mechanisms governing psoriasis pathogenesis, with CXCL10 in particular being identified as a promising biomarker of this debilitating disease.

Materials And Methods

Data collection and preprocessing

Raw gene expression profile data (cel files) for the GSE13355 (58 lesional skin samples, 64 normal skin samples), GSE30999 (82 lesional skin samples, 82 normal skin samples), and GSE106992 (125 lesional

skin samples, 67 normal skin samples) datasets were downloaded from the GEO database [11]. Hallmark gene sets were downloaded from the Molecular Signatures Database (MSigDB) [12]. Drug sensitivity data were downloaded from the cellminer Database [13].

DEG identification

DEGs were identified and plotted using R 3.6.2 with the Affy [14] and Limma packages [15]. DEGs were those meeting the following criteria: Adjusted $P < 0.05$, $\log |FC| > 1.0$.

Principal component analysis

A multivariate principal component analysis (PCA) [16] was used to differentiate between samples. For this analysis, DEGs were treated as variables, and differences between healthy and psoriatic skin samples were identified.

Functional enrichment analyses

Gene Ontology (GO) [17] and Kyoto Encyclopedia of Genes and Genomes (KEGG) [18] enrichment analyses were conducted with the R clusterProfiler package [19] in an effort to clarify the functional roles of identified DEGs in psoriasis. Enrichment was considered significant at a threshold of $P < 0.05$.

Gene set variation analysis (GSVA)

GSVA analyses evaluate pathway and biological process activity over a sample population in an unsupervised manner [20]. The “c2.cp.kegg.v6.2.symbols” and “h.all.v6.2.symbols” gene set files from the Molecular Signatures Database were used to conduct the GSVA analysis with the GSVA R package. $P < 0.05$ was the significance threshold for this analysis.

Protein-protein interaction (PPI) network construction

The STRING database (<http://string-db.org>)(v 10.0) [21] was used to construct a PPI network incorporating psoriasis-related DEGs with a combined interaction score > 0.4 . The network was visualized with the open-source Cytoscape program (v 3.4.0) [22].

The plug-in Molecular Complex Detection (MCODE) (version 1.4.2) of Cytoscape is an APP for clustering a given network based on topology to find densely connected regions. The PPI networks were drawn using Cytoscape and the most significant module in the PPI networks was identified using MCODE. The criteria for selection were as follows: MCODE scores > 5 , degree cut-off = 2, node score cut-off = 0.2, Max depth = 100 and k-score = 2.

Hub genes selection and analysis

The hub genes were selected with degrees ≥ 10 . A network of the genes and their co-expression genes was analyzed using Cytoscape. The CytoHubba plugin in Cytoscape and molecular complex detection (MCODE) were employed to identify hub genes.

ceRNA network construction

Interactions between lncRNAs and miRNAs were predicted using miRcode [23]. StarBase was used to predict mRNA targets of miRNAs of interest [24], along with miRDB[25], and miRWalk[26]. Those interactions that were predicted by all three databases were the focus of interactions between miRNAs and psoriasis-related DEGs. A lncRNA/miRNA/mRNA ceRNA network was then constructed based on these predicted interactions, with the resultant network being visualized with the Cytoscape software[22].

ROC analysis

Receiver operating characteristic (ROC) curve analyses were used to assess the diagnostic performance of particular DEGs as a means of differentiating between psoriatic and normal samples based on area under the ROC curve (AUC) values [27]. These analyses were conducted with the R pROC package, with the value yielding the maximum sum of sensitivity and specificity serving as a cut-off value[28].

Drug Sensitivity Analysis

Drug sensitivity data were downloaded from GDSC, and the relationships between gene expression and putative psoriasis drug sensitivity were analyzed.

Immune infiltration analysis

The CIBERSORT database was used to evaluate the relationship between genes and immune cell infiltration profiles in normal and psoriatic samples in these three datasets [29]. The resultant data were visualized using bar charts, correlation charts, violin plots, and heatmaps. Correlations between hub genes and infiltrating immune cell populations in these three datasets were assessed, and samples were stratified into those that exhibit low or high levels of a given gene of interest based on the median expression value for that gene. Box plots were then used to visualize differences in the degree of immune cell infiltration by particular cell types between these high and low expression sample cohorts.

Statistical analysis

Data are means $\pm$ standard deviation, and were analyzed using R (v.3.6.2), with $P < 0.05$ as the significance threshold.

Results

Principal component analysis and distribution density mapping of psoriasis-related differentially expressed genes

We began by plotting distribution density maps for sample gene expression data from the GSE13355, GSE30999, and GSE106992 datasets (Fig. 1A-C), revealing similar expression profiles for both control and lesional samples in all cases, suggesting that sufficient data were available to permit variance analysis. Subsequent PCA revealed that control and lesional samples from these three datasets could be separated by the chosen DEGs, indicating that screened DEG expression patterns were specific and associated with psoriasis (Fig. 1D-F).

Differential gene expression analysis

Next, we identified DEGs in these three datasets using the R limma package, including 655, 849, and 286 DEGs in the GSE13355, GSE30999, and GSE106992 datasets, respectively. The resultant data were then subjected to heatmap and clustering analyses, which revealed clear and reliable differentiation between the control and psoriasis samples (Fig. 2A, C, E). Volcano plots additionally highlighted differences between groups with respect to DEG expression (Fig. 2B, D, F).

Functional enrichment analyses

Next, the 197 DEGs that were shared across these three datasets were next identified and used to conduct functional enrichment analyses (Fig. 3). GO terms significantly enriched for these genes included BPs such as response to virus, defense response to virus, antimicrobial humoral response, type 1 interferon signaling pathway, and cellular response to type 1 interferon (Table 1A). Enriched CCs included cornified envelope, specific granule lumen, tertiary granule lumen, secretory granule lumen, and cytoplasmic vesicle lumen (Table 1B). Enriched MFs included chemokine receptor binding, serine-type endopeptidase activity, serine-type peptidase activity, serine hydrolase activity, and chemokine activity (Table 1C). KEGG pathways revealed these DEGs to be enriched in 5 pathways, including the IL-17 signaling pathway (11 genes, hsa04657), the NOD-like receptor signaling pathway (14 genes, hsa04621), the Viral protein interaction with cytokine and cytokine receptor pathway (10 genes, hsa04061), the influenza A pathway (11 genes, hsa05164), and the cytokine-cytokine receptor interaction pathway (13 genes, hsa04060) (Table 1D). While the specific genes enriched in these pathways for each dataset were not identical, all three datasets were nonetheless enriched in the same pathway (Table 2).

GSVA analysis

The hallmark gene set was next selected as a reference set, after which a GSVA approach was used to assess differences in pathway enrichment between control and psoriatic samples in these three datasets. This analysis revealed that there were differences in the relative degree of pathway enrichment for different datasets, although the overall trends remained the same as above (Fig. 4).

Protein-protein interaction network

Next, interactions among these 197 DEGs were assessed by generating a PPI network with the STRING database (Table 3A). An interaction network diagram for these genes was additionally generated (Fig. 5A), and the MCODE plugin was used to select cluster 1 (Fig. 5B; Table 3B). The cytoHubba tool was then used to identify key hub genes within this cluster (Fig. 5C), leading to the identification of 10 key hub genes, with darker coloration corresponding to a higher degree value (Table 3C). A one-step interaction node for these 10 genes was then prepared (Fig. 5D). Those 6 genes that overlapped between the MCODE and cytoHubba hub gene analyses (CXCL10, IRF7, IFIT3, OAS1, GBP1, ISG15) were then identified as putative biomarkers of psoriasis (Table 4).

ceRNA network construction

The predictions made by the starBase, miRDB, and miRWalk databases were next integrated to identify putative miRNAs targeting these hub genes. StarBase was then further used to predict lncRNAs interacting with these miRNAs, facilitating the construction of a ceRNA network (Fig. 6).

Assessment of hub gene diagnostic accuracy

ROC curve analyses were next used to gauge the diagnostic accuracy of CXCL10, IRF7, IFIT3, OAS1, GBP1, and ISG15 (Fig. 7). The AUC values for these ROC curves were 0.959, 0.966, 1, and 0.98 for GSE13355 (Fig. 7A-F), while for GSE30999 they were 0.968, 0.963, 0.961, and 0.954 (Fig. 7G-L), and for GSE106992. they were 0.831, 0.835, 0.789, and 0.833 (Fig. 7M-R).

Drug sensitivity analysis

Next, drug sensitivity analyses were conducted for these six hub genes (Fig. 8). The results of these analyses suggested that certain drugs were negatively and positively correlated with the expression of these hub genes, with positive correlations indicating that a patient is more likely to be sensitive to a given drug if the corresponding gene is upregulated, and negative correlations indicating the opposite. In total, sensitivity to 10 different drugs was predicted to be increased ($P < 0.05$), including LDK-378, AP-26113, Alectinib, Lenvatinib, Tanespimycin, Pazopanib, Elesclomol, Estramustine, Abiraterone, Idelalisib, and Itraconazole.

Immune cell infiltration analysis

Lastly, we used the CIBERSORT algorithm to assess immune cell infiltration for each of these three datasets, assessing the immune cell composition of each sample, correlations between immune cell populations, and differences in immune cell levels between normal and diseased samples as represented using heatmaps and violin plots (Fig. 9).

We then conducted correlation analyses to examine the relationships between the hub genes identified above and immune cell infiltration in these three datasets, revealing significant differences in immune cell levels between samples with low and high levels of hub gene expression (Fig. 10).

Discussion

Psoriasis is an autoimmune inflammatory skin disease with a chronic etiology that impacts an estimated 0.96 per 1,000 people in Europe [30]. Psoriatic lesions can manifest as systemic or localized regions of scaly erythema and plaques, primarily in younger adults. There are four primary clinical types of psoriasis: ordinary, arthritis, pustular, and erythroderma, with the ordinary type accounting for over 99% of the total psoriasis disease burden. This disease generally exhibits a recurrent, chronic course that adversely impacts many aspects of individual physical and mental health, interfering with social interactions and other facets of daily life. In one survey, 79% of psoriasis patients reported that the disease had negatively impacted their lives, with 10% having contemplated suicide [31]. Current therapeutic targets associated with psoriasis include TNF- α , PDE-4, T cells, VEGF, and a range of signaling molecules, with many inhibitors targeting these pathways having been developed and marketed

to date. Identifying novel biomarkers of psoriasis has the potential to improve patient quality of care and cost of treatment by facilitating the development of highly specific, inexpensive, and efficient treatments. Herein, we explored psoriasis-related gene expression patterns through a microarray-based bioinformatic analysis of three GEO gene expression profiles, leading to the identification of 197 DEGs associated with psoriasis incidence.

Identified DEGs were enriched for pathways including NOD-like receptor signaling, IL-17 signaling, cytokine-cytokine receptor interactions, Influenza A, viral protein interaction with cytokine and cytokine receptors, hepatitis C, drug metabolism-other enzymes, and biosynthesis of unsaturated fatty acids pathways. This analysis revealed a close relationship between IL-17 and psoriasis, consistent with prior reports highlighting a key role for this cytokine in psoriatic disease progression. IL-17 mRNA levels are elevated in psoriatic skin samples relative to normal skin [32]. Treatment of keratinocytes with IL-17 can further promote the upregulation of pro-inflammatory cytokines including IL-6 and IL-8, thereby potentially exacerbating psoriasis[33]. The topical application of the TLR7/8 ligand imiquimod can induce IL-17A and IL-17F expression and drive psoriasis-like dermatitis in mice [34]. Treatment with CsA and anti-TNF- α drugs can further decrease IL-17A, IFN- γ , IL-23p19, and CCL20 levels in psoriatic lesions while improving psoriatic eruptions, [33,35-37], suggesting that IL-17A and other proinflammatory cytokines play key roles in psoriasis development.

In our PPI network analysis, we identified CXCL10 as having the highest degree value, while IRF7, IFIT3, OAS1, GBP1, and ISG15 were identified as key targets for the drug-based treatment of psoriasis. Targeting CXCL10 may thus be a viable approach to treating this debilitating disease. The upregulation of CXCL10 has been detected in many Th1 inflammatory diseases in humans [38]. Reductions in serum CXCL10 levels over time have been reported to be related to new-onset psoriatic arthritis in psoriasis patients [39]. We found that CXC family cytokines including CXCL1, CXCL9, and CXCL10 were primarily enriched in skin- and cytokine signaling-related GO and KEGG pathways, suggesting a potential role for these factors as regulators of psoriasis. Luster et al. previously highlighted the relationship between chemokines and inflammation, likely explaining their predicted role in psoriasis patients [40]. IRF7, IFIT3, OAS1, GBP1, and ISG15 were also identified as promising targets for the treatment of psoriasis. Raposo et al. detected significant upregulation of 16 different antiviral genes in lesional psoriatic skin, with ISG15 expression being increased more than two-fold [41], and others have similarly observed cutaneous upregulation of antiviral proteins in the context of psoriasis [42], potentially explaining why these patients rarely experience cutaneous viral infections. Psoriasis is also associated with keratinocyte expansion, and these cells may express high levels of antiviral genes. Immune cells also express high levels of these antiviral genes [41], potentially indicating robust immune cell and keratinocyte activity in this pathological context. Consistently, analyses of the CIBERSORT database suggested that these 6 hub genes were associated with infiltration by 22 different immune cell types. Together, these results offer new insights into biomarkers and pathways that may be targeted to more effectively treat psoriasis.

There are several limitations to this analysis. For one, integrated analyses of blood samples that were not conducted in the present study are required to more fully clarify the molecular mechanisms governing

psoriasis. Secondly, an individual microarray analysis has the potential to yield false-positive results that cannot be replicated. As such, it is essential that multiple individual datasets be integrated together to facilitate a more robust analysis of the genetic basis for psoriasis. Third, additional mechanistic experiments including western blotting, qPCR, and immunohistochemical assays will be required to clarify the functional importance of the hub genes identified in this study as regulators of psoriasis development and progression.

Conclusions

In summary, we conducted the present study to identify key genes likely to be involved in psoriasis development or progression. This led us to identify 197 key psoriasis-related DEGs, with CXCL10 representing a particularly promising biomarker worthy of future study as a sensitive indicator of psoriasis. However, further research will be needed to understand the biological role of this chemokine in patients with this condition, and to validate the results of this study so as to improve patient care.

Abbreviations

GEO: Gene Expression Omnibus; DEGs: Differentially expressed genes;

GO: Gene ontology; KEGG: Kyoto Encyclopedia of Genes and Genomes;

PPI: Protein-protein interaction; IRF7: Interferon Regulatory Factor 7; IFIT3: Interferon Induced Protein With Tetratricopeptide Repeats 3; OAS1: Oligoadenylate Synthetase 1; GBP1: Guanylate Binding Protein 1

Declarations

Acknowledgements

Not applicable.

Authors' contributions

ST and JL designed the current study, performed data analysis and wrote the manuscript. PX and YY performed the literature review regarding cytokines in psoriasis. JL and SX analyzed the data. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analysed during this study are included in this published article.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table I. GO and KEGG pathway enrichment analysis of DEGS in psoriasis samples.

A GO-BP				
ID	Description	Count in gene set	pvalue	p.adjust
GO:0009615	response to virus	24	4.14E-15	8.50E-12
GO:0051607	defense response to virus	21	6.71E-15	8.50E-12
GO:0019730	antimicrobial humoral response	16	2.57E-14	2.17E-11
GO:0060337	type I interferon signaling pathway	14	2.16E-13	1.09E-10
GO:0071357	cellular response to type I interferon	14	2.16E-13	1.09E-10
B GO-CC				
ID	Description	Count in gene set	pvalue	p.adjust
GO:0001533	cornified envelope	10	3.25E-10	6.44E-08
GO:0035580	specific granule lumen	7	1.41E-06	0.000139
GO:1904724	tertiary granule lumen	6	9.99E-06	0.00066
GO:0034774	secretory granule lumen	11	0.000167	0.00828
GO:0060205	cytoplasmic vesicle lumen	11	0.000261	0.008832
C GO-MF				
ID	Description	Count in gene set	pvalue	p.adjust
GO:0042379	chemokine receptor binding	11	4.60E-11	1.81E-08
GO:0004252	serine-type endopeptidase activity	14	7.18E-10	1.42E-07
GO:0008236	serine-type peptidase activity	14	3.88E-09	5.06E-07
GO:0017171	serine hydrolase activity	14	5.14E-09	5.06E-07
GO:0008009	chemokine activity	8	2.60E-08	1.85E-06
D KEGG				
ID	Description	Count in gene set	pvalue	p.adjust
hsa04657	IL-17 signaling pathway	11	2.41E-08	3.66E-06
hsa04621	NOD-like receptor signaling pathway	14	5.84E-08	4.44E-06
hsa04061	Viral protein interaction with cytokine and cytokine receptor	10	4.86E-07	2.46E-05
hsa05164	Influenza A	11	1.02E-05	0.000388

hsa04060	Cytokine-cytokine receptor interaction	13	8.77E-05	0.002666

Table II. KEGG pathway enrichment analysis of DEGS in the most significant module

A GSE13355				
Pathway	logFC	P.Value	adj.P.Val	
HALLMARK_INFLAMMATORY_RESPONSE	0.352579	3.23E-26	1.61E-24	
HALLMARK_MYC_TARGETS_V2	0.602905	6.78E-26	1.69E-24	
HALLMARK_NOTCH_SIGNALING	-0.44874	5.03E-25	8.39E-24	
HALLMARK_ALLOGRAFT_REJECTION	0.414567	5.10E-24	6.38E-23	
HALLMARK_UV_RESPONSE_DN	-0.43353	1.84E-23	1.84E-22	
HALLMARK_MTORC1_SIGNALING	0.530295	1.01E-20	8.45E-20	
HALLMARK_E2F_TARGETS	0.523939	1.35E-19	9.68E-19	
HALLMARK_INTERFERON_GAMMA_RESPONSE	0.379394	5.10E-16	3.18E-15	
HALLMARK_COMPLEMENT	0.240224	2.41E-13	1.34E-12	
HALLMARK_MYOGENESIS	-0.26514	3.02E-13	1.51E-12	
B GSE30999				
Pathway	logFC	P.Value	adj.P.Val	
HALLMARK_MTORC1_SIGNALING	0.474102	2.18E-26	1.09E-24	
HALLMARK_MYOGENESIS	-0.31789	1.96E-25	4.89E-24	
HALLMARK_E2F_TARGETS	0.512633	4.52E-25	7.53E-24	
HALLMARK_MYC_TARGETS_V2	0.496877	5.57E-22	6.96E-21	
HALLMARK_INTERFERON_GAMMA_RESPONSE	0.364591	1.03E-20	1.03E-19	
HALLMARK_UV_RESPONSE_DN	-0.36363	3.28E-20	2.73E-19	
HALLMARK_COMPLEMENT	0.251523	3.85E-18	2.75E-17	
HALLMARK_INFLAMMATORY_RESPONSE	0.272044	3.23E-16	2.02E-15	
HALLMARK_EPITHELIAL_MESENCHYMAL_TRANSITION	-0.39572	1.07E-15	5.97E-15	
HALLMARK_ALLOGRAFT_REJECTION	0.309652	9.69E-15	4.84E-14	
C GSE106992				
Pathway	logFC	P.Value	adj.P.Val	
HALLMARK_INTERFERON_GAMMA_RESPONSE	0.290468	5.35E-13	2.68E-11	
HALLMARK_ALLOGRAFT_REJECTION	0.259119	3.51E-11	8.78E-10	
HALLMARK_MYOGENESIS	-0.19898	3.61E-10	6.02E-09	

HALLMARK_MYC_TARGETS_V2	0.325852	1.53E-09	1.92E-08
HALLMARK_COMPLEMENT	0.169069	2.66E-09	2.66E-08
HALLMARK_UV_RESPONSE_DN	-0.23263	6.57E-09	5.36E-08
HALLMARK_MTORC1_SIGNALING	0.278927	7.50E-09	5.36E-08
HALLMARK_NOTCH_SIGNALING	-0.21364	5.98E-08	3.74E-07
HALLMARK_ADIPOGENESIS	-0.17391	1.97E-07	9.86E-07
HALLMARK_E2F_TARGETS	0.279246	1.97E-07	9.86E-07

Table III. Top 10 hub genes with DEGs degree from the PPI network.

A PPI-top10		
node1	node2	combined_score
ABCA12	TGM1	0.802
ABCA12	SPTLC2	0.412
ABCA12	CNFN	0.401
ABCA12	TGM3	0.403
ABCA12	IL36RN	0.459
ABCA12	PRSS27	0.482
ABCA12	IVL	0.522
ABCA12	ALOX12B	0.768
ACOT1	ACOT2	0.962
ACOT1	HAO2	0.46
B MCODE-top10		
MCODE_Cluster	MCODE_Score	name
Cluster 1	18	HERC6
Cluster 1	18	IFI6
Cluster 1	18	OAS2
Cluster 1	18	RSAD2
Cluster 1	18	OAS1
Cluster 1	18	OAS3
Cluster 1	18	MX1
Cluster 1	18	CMPK2
Cluster 1	18	IFIT1
Cluster 1	18	ISG15
C cytoHubba-top10		
MCODE_Cluster	MCODE_Score	name
Cluster 2	8	CCL20
Cluster 1	18	ISG15
Cluster 2	8	CXCL1

Cluster 2	10	CXCL9
Cluster 1	18	GBP1
Cluster 1	18	OAS1
Cluster 1	18	IFIT3
Cluster 1	18	CXCL10
Cluster 2	8	CXCL8
Cluster 1	18	IRF7

Table IV. Functional roles of 6 hub genes with degree ≥ 10 .

Gene symbol	Full name	Funtion	Pathway
CXCL10	C-X-C Motif Chemokine Ligand 10	Pro-inflammatory cytokine that is involved in a wide variety of processes such as chemotaxis, differentiation, and activation of peripheral immune cells, regulation of cell growth, apoptosis and modulation of angiostatic effects	GO:0005102 GO:0005125 GO:0005515 GO:0008009 GO:0008201
IRF7	Interferon Regulatory Factor 7	Key transcriptional regulator of type I interferon (IFN)-dependent immune responses and plays a critical role in the innate immune response against DNA and RNA viruses.	GO:0000978 GO:0000981 GO:0000987 GO:0003677 GO:0003700
IFIT3	Interferon Induced Protein With Tetratricopeptide Repeats 3	IFN-induced antiviral protein which acts as an inhibitor of cellular as well as viral processes, cell migration, proliferation, signaling, and viral replication. Enhances MAVS-mediated host antiviral responses by serving as an adapter bridging TBK1 to MAVS which leads to the activation of TBK1 and phosphorylation of IRF3 and phosphorylated IRF3 translocates into nucleus to promote antiviral gene transcription	GO:0003674 GO:0003723 GO:0005515 GO:0042802
OAS1	2'-5'-Oligoadenylate Synthetase 1	Interferon-induced, dsRNA-activated antiviral enzyme which plays a critical role in cellular innate antiviral response. In addition, it may also play a role in other cellular processes such as apoptosis, cell growth, differentiation and gene regulation.	GO:0000166 GO:0001730 GO:0003723 GO:0003725 GO:0005515
GBP1	Guanylate Binding Protein 1	Hydrolyzes GTP to GMP in 2 consecutive cleavage reactions. Exhibits antiviral activity against influenza virus. Promotes oxidative killing and delivers antimicrobial peptides to autophagolysosomes, providing broad host protection against different pathogen classes.	GO:0000166 GO:0003779 GO:0003924 GO:0005515 GO:0005525
ISG15	ISG15 Ubiquitin Like Modifier	Ubiquitin-like protein which plays a key role in the innate immune response to viral infection either via its conjugation to a target protein (ISGylation) or via its action as a free or unconjugated protein.	GO:0005178 GO:0005515 GO:0031386

Figures

Figure 1

The distribution density map and the principal component analysis of the three datasets. (A) GSE13355 distribution density map. (B) GSE30999 distribution density map. (C) GSE106992 distribution density map. (D) GSE13355 principal component analysis. (E) GSE30999 principal component analysis. (F) GSE 106992 principal component analysis.

Figure 2

DEGs identified by microarray assay between psoriatic and NN skin. (A, C, E) Heat maps of DEGs in GSE13355, GSE30999 and GSE106992. (D, E, F) Volcano plots of DEGs in GSE13355, GSE30999 and GSE106992. Volcano plots show the $-\log_{10}Q$ -values against logFC for DEGs in the skin, in which the green, red, and gray points represent down-expressed, upexpressed, and not DEGs, respectively.

Figure 3

GO and KEGG analysis of 197 DEGs. (A-C) Chord plot indicates the relationship between genes and KEGG pathways in GSE13355. (D) Significantly enriched pathway terms of DEGs in GSE13355. (E-G) Chord plot indicates the relationship between genes and KEGG pathways in GSE30999. (H) Significantly enriched pathway terms of DEGs in GSE30999. (I-K) Chord plot indicates the relationship between genes and KEGG pathways in GSE106992. (L) Significantly enriched pathway terms of DEGs in GSE106992.

Figure 4

Gene set variation analysis (GSVA) of hallmark genes in three datasets. (A) GSVA in GSE13355 dataset. (B) GSVA in GSE30999 dataset. (C) GSVA in GSE106992 dataset.

Figure 5

PPI network and the most significant module of DEGs. (A) The PPI network of DEGs was constructed using Cytoscape. (B) The most significant module was obtained from PPI network with 20 nodes. Upregulated genes are marked in light red; downregulated genes are marked in light blue. (C) Top 10 hub genes with DEGs degree from the PPI network. (D) Hub genes and their co-expression genes were analyzed using cytoHubba.

Figure 6

Construction of ceRNA network in 6 hub genes. (A) CeRNA network in CXCL10. (B) CeRNA network in IRF7. (C) CeRNA network in IFIT3. (D) CeRNA network in OAS1. (E) CeRNA network in GBPI. (F) CeRNA network in ISG15.

Figure 7

ROC curve analysis of 6 hub genes in three datasets. (A-F) The areas under the ROC curves were 0.95, 0.959, 0.966, 1, 0.98 and 0.989 for GSE13355. (G-L) The areas under the ROC curves were 0.92, 0.968, 0.963, 0.961, 0.954 and 0.977 for GSE30999. (M-R) The areas under the ROC curves were 0.76, 0.831, 0.835, 0.789, 0.833 and 0.795 for GSE106992.

Figure 8

Drug sensitivity analysis of 6 hub genes. The sensitivity to 10 drugs were increased ($P \leq 0.05$), including LDK-378, AP-26113, Alectinib, Lenvatinib, Tanespimycin, Pazopanib, Elesclomol, Estramustine, Abiraterone, Idelalisib and Itraconazole. * $P \leq 0.05$; ** $P \leq 0.01$.

Figure 9

Immune infiltration analysis in three datasets. (A, E, I) Immune cell analysis of GSE13355, GSE30999 and GSE 106992 was shown in the bar graph. (B, F, G) The correlation of the expression of immune cells in GSE13355, GSE30999 and GSE 106992 was analyzed. (C, G, K) The difference in the expression of immune cells between disease and normal samples was analyzed, as shown in the heat map. (D, H, L) The difference in the expression of immune cells between disease and normal samples was analyzed, as shown in the violin plot.

Figure 10

Correlation analysis of Immune infiltration of 6 hub genes. (A-F) Correlation analysis of immune infiltration of 6 hub genes in GSE13355. (G-L) Correlation analysis of immune infiltration of 6 hub genes in GSE30999. (M-R) Correlation analysis of immune infiltration of 6 hub genes in GSE106992.