Original Article

The long non-coding RNA and mRNA expression profiles in keratinocytes from patients with psoriasis vulgaris

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Background: Psoriasis is a chronic inflammatory dermatosis. The hyperproliferation and hyperkeratosis of keratinocytes is a key step in the pathogenesis of psoriasis. Long non-coding RNAs (lncRNAs) and mRNAs regulate gene expression in various biological process, including the function of keratinocytes. This research investigated the expression profile of lncRNAs and mRNAs in keratinocytes of patients with psoriasis vulgaris.

Methods: The expression of lncRNAs and mRNAs in keratinocytes from patients with psoriasis vulgaris and healthy patients was examined and compared using microarrays. Quantitative polymerase chain reaction (qPCR) and bioinformatic analysis was also performed. DAVID and KEGG were used to analyze the gene function. The competing endogenous RNA (ceRNA) network was also constructed.

Results: A total of 48 lncRNAs and 17 mRNAs were differentially expressed in keratinocytes of psoriasis vulgaris. Quantitative PCR data showed that the expression of lnc-AGXT2L1-2:2 (P=0.009) and NR_027032 (P=0.033) was up-regulated in psoriasis vulgaris. The lncRNA-miRNA-mRNA interaction network was established. The mRNA showing the most connections with the lncRNAs and miRNAs was CEP104. The miRNA showing the most connections with the lncRNAs and mRNAs was miR-484. The lncRNA showing the most connections with miRNAs and mRNAs was ENST00000494887.

Conclusions: The identification of the differentially expressed lncRNAs and mRNAs in psoriasis vulgaris provides significant insights into the pathogenesis of the disease.

Keywords: Expression profile; keratinocytes; long non-coding RNA (lncRNA); mRNA; psoriasis vulgaris

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Introduction

Psoriasis is a chronic inflammatory dermatosis. Due to the unknown etiology and lack of effective treatments, the course of the disease is generally prolonged and recurring, and significantly affects the quality of life of these patients (1). The incidence and prevalence vary greatly between different ethnic backgrounds and geographic regions. In China, psoriasis affects approximately 0.1% to 0.5% of the population (2). Psoriasis can be divided into four subtypes based on the clinical characteristics, namely, psoriasis vulgaris, psoriasis arfhropathica, psoriasis pustulose, and erythrodermic psoriasis. Psoriasis vulgaris is the most common clinical type and accounts for about 85–90% of all cases (3).

The pathogenesis of psoriasis is complex. The disease is specific genetic susceptible and characterized by various exogenous or endogenous stimulation signals. It is generally

Table 1 The clinical characteristics of patients with psoriasis vulgaris

Gender	Age	PASI
Female	27	36
Female	40	35
Male	33	41.4
Female	48	25.2
Male	58	24
Male	21	16.8
Male	35	49.9
Male	54	53.9
Male	40	29.7
Male	52	14.4
Male	53	23.4
Female	45	44.1
Female	42	21.6
Male	26	21
Female	64	36

PASI, psoriasis lesion area and severity score.

believed that the abnormal activation of immunocytes, especially T cells, is involved in the pathogenesis of psoriasis. The infiltration of immunocytes within the skin triggers the expression of cytokines and induces the abnormal proliferation and activation of keratinocytes (4). The resultant associated skin damage is characteristic of psoriasis vulgaris patients

During various biological processes, non-coding RNAs, especially long non-coding RNAs (lncRNAs), can act as modulators of gene expression. Recent studies have shown that non-coding RNAs are key to the occurrence and development of psoriasis through regulating the expression of important proteins. The non-coding RNA PRINS mediates abnormal keratinocyte proliferation in patients with psoriasis by regulating the expression of the G1P3 protein (5). In addition, microRNA(miRNA)-31 promotes keratinocyte proliferation by inhibiting protein phosphatase 6 (6). In 2018, Qiao *et al.* found that lnc-MSX2P1 promoted the growth and proliferation of keratinocytes through the suppression of miR-6731-5p and the activation of the S100A7 gene. It was suggested that the lnc-MSX2P1-miR-6731-5p-S100A7 axis participates in the abnormal proliferation of keratinocytes in psoriasis (7). All these studies suggested that non-coding RNAs are closely related to the abnormal proliferation of keratinocytes. The different categories of non-coding RNAs are not isolated, and can form a complex regulatory network to participate in disease regulation. Therefore, elucidating the role of non-coding RNAs in psoriasis will be beneficial in improving the understand of the pathogenesis of the disease. This current study examined the lncRNA and mRNA expression profiles of keratinocytes in patients with psoriasis vulgaris. We present the following article in accordance with the MDAR reporting checklist (available at https://dx.doi.org/10.21037/apm-21-2046).

Methods

Patients

A total of 15 patients with progressive psoriasis vulgaris were recruited from Huashan Hospital, Fudan University, China. The healthy skin control group consisted of 15 age-matched and gender-matched patients who underwent plastic surgery in the same hospital . Patients with psoriasis did not take internal medicine for 3 months and did not use external drugs for 1 month prior to this study. The psoriasis lesion area and severity score (PASI) of patients with psoriasis is listed in *Table 1*. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Ethics Committee of Huashan Hospital (NO.: 2019-541) and informed consent was taken from all the patients.

Human epidermal keratinocyte culture

Skin samples were acquired from the skin lesions of participants with psoriasis vulgaris. Negative controls were acquired from the healthy skin of patients who underwent plastic surgery. The skin samples were incubated overnight at 4 ℃ in Dispase solution (Roche life science products). The epidermis was separated using the trypsin digestion method. Keratinocytes were cultured in keratinocyte serum-free complete medium. The second or third generation of keratinocytes was used for RNA isolation.

RNA isolation and quantitative analysis

Total RNA was isolated and purified using the Qiagen Kit (Germany). Quantitative reverse transcription (RT)-polymerase chain reaction (PCR) was performed according

Table 2 The primer sequences used in the quantitative polymerase chain reactions

Primer Name	Sequence (5' to 3')
Actin-F	ACCATTGGCAATGAGCGGTT
Actin-R	GCGGATGTCCACGTCACACT
lnc-AGXT2L1-2:2-F	TATAACTGCTATTCTTGCAGCCCTT
lnc-AGXT2L1-2:2-R	TCCCATAGGACCATCTGTACCC
NR_027032-F	TCAAAGTTTTCCTCTGAGTGG
NR_027032-R	AAGCAGGTAACAAGTGGGGA
NR_004407-F	AACTCGATTGCTCTGCGTGC
NR_004407-R	CACCAGCTGCCCAAATACCA
ENST00000528514-F	AAGGTTGGCTTCAGAACTGG
ENST00000528514-R	GTTCCCGTTGGTTTTTCTTG

to the manufacturer's instructions. The primers are listed in *Table 2*.

LncRNA and mRNA microarray

LncRNA and mRNA microarrays were performed according to the manufacturer's protocols (Agilent technologies, Santa Clara, US). All data has been deposited into the Gene Expression Omnibus (GEO) with accession number GSE146149.

Analysis of gene function

Gene molecular function was analyzed through the Database for Annotation, Visualization and Integrated Discovery (DAVID). The roles of the genes in the pathways were analyzed by the Kyoto Encyclopedia of Genes and Genomes (KEGG) database.

Construction of the competing endogenous RNA (ceRNA) network

Data regarding miRNAs related to the differentially expressed lncRNAs and mRNAs was downloaded from miRBase using miRanda software.

Statistical analysis

The Student's *t*-test was applied for statistical analyses and P<0.05 was considered statistically significant.

Results

The expression profile of lncRNAs in keratinocytes of patients with psoriasis vulgaris

The expression profile of lncRNAs in keratinocytes obtained from psoriasis vulgaris patients was compared to that of healthy controls using a genome-wide analysis. Hierarchical cluster analysis revealed significant differences in the expression of 48 lncRNAs (including 9 upregulated lncRNAs and 39 downregulated lncRNAs) in the keratinocytes of psoriasis vulgaris patients and healthy patients (fold change ≥1.5; P<0.05; *Figure 1A*). The 48 differentially expressed lncRNAs were divided into 6 classes, including 23 intergenic lncRNAs, 11 exonic-sense, 6 exonic-antisense, 4 intronic-sense, 2 intronic-antisense, and 2 bidirectional lncRNAs (in total online: https://cdn.amegroups.cn/static/public/apm-21-2046-1.xlsx).

The expression profile of mRNAs in keratinocytes of patients with psoriasis vulgaris

Significant differences were identified in the expression of 17 mRNAs (fold change ≥1.5, P<0.05) in psoriasis vulgaris keratinocytes compared with healthy keratinocytes (*Figure 1B*), including 3 up-regulated mRNAs and 14 downregulated mRNAs (in total online: https://cdn.amegroups.cn/static/public/apm-21-2046-2.xlsx). Gene ontology (GO) analysis revealed that the differentially expressed mRNAs could be classified into three domains. In the biological process domain, the top three GO terms were cation transport, ion transport, and small molecule metabolic process (*Figure 2A*). In the molecular function domain, the top three GO terms included organic cyclic compound binding, nucleic acid binding, and small molecule binding (*Figure 2B*). The top three GO terms in the cellular component domain were intracellular, intracellular organelle, and cytoplasm (*Figure 2C*). KEGG pathway analysis was performed to identify the important signaling pathways and the interactions associated with the 17 differentially expressed mRNAs. There were 11 signaling pathways enriched in keratinocytes of patients with psoriasis vulgaris. The top 5 pathways identified were mismatch repair, African trypanosomiasis, malaria, aminoacyl-tRNA biosynthesis, and antigen processing and presentation (*Figure 2D*).

Confirmation of the differentially expressed lncRNAs

Four differentially expressed lncRNAs were randomly

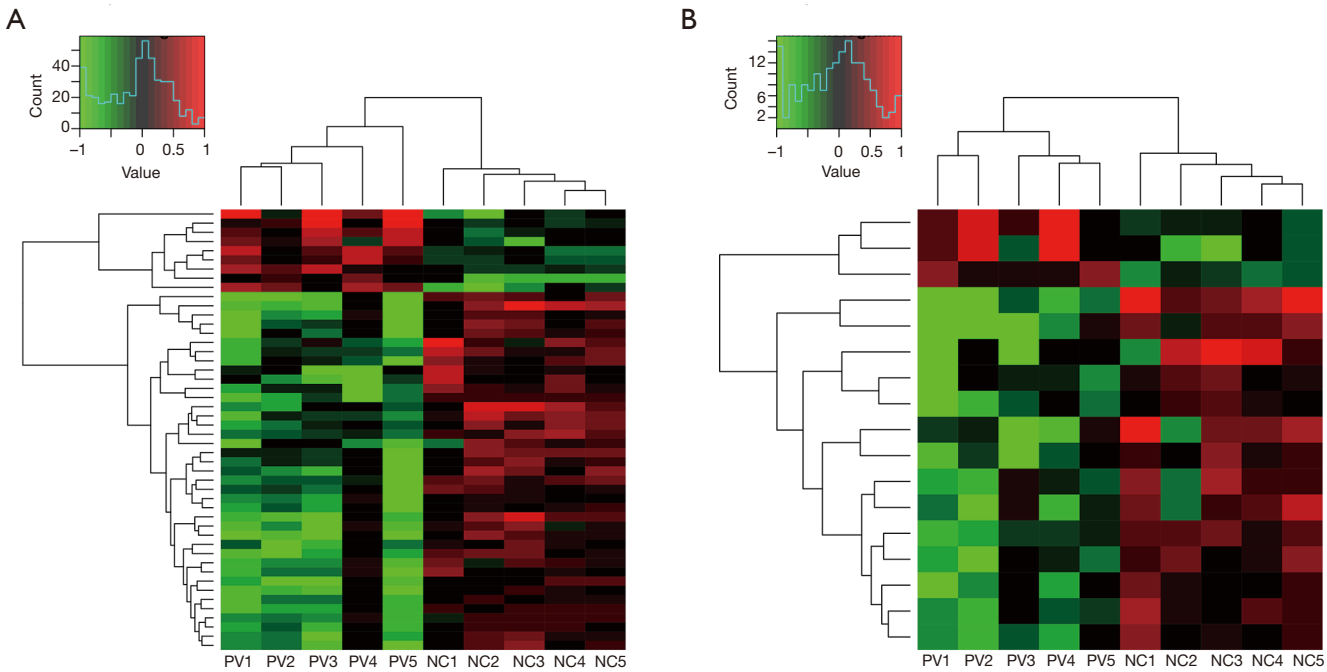

Figure 1 Hierarchical clusters of differentially expressed long non-coding RNAs (lncRNAs) and mRNAs. (A) Significant differences in the expression of 48 lncRNAs (9 upregulated lncRNAs and 39 downregulated lncRNAs) were found in psoriasis vulgaris keratinocytes (n=5) compared with normal controls (n=5) (fold change ≥1.5; P<0.05). (B) Significant differences in the expression of 17 mRNAs (fold change ≥1.5; P<0.05) were identified in psoriasis vulgaris keratinocytes (n=5) compared with healthy controls (n=5), including 3 up-regulated mRNAs and 14 downregulated mRNAs (fold change ≥1.5; P<0.05). In (A) and (B), relatively high expression is indicated by red shading and relatively low expression is indicated by green shading. NC1-5 represents normal controls. PV1-5 represents patients with psoriasis vulgaris.

selected for qRT-PCR analysis to verify the reliability of the microarray results. The expression of lnc-AGXT2L1-2:2 and NR_027032 was up-regulated in keratinocytes from psoriasis vulgaris patients compared to healthy keratinocytes , which was consistent with the results of the microarray. However, there were no statistically significant differences in the expression of NR_004407 nor ENST00000528514 between psoriasis vulgaris keratinocytes compared to healthy keratinocytes, although there was a similar trend to that observed in the microarray analysis (*Figure 3*).

LncRNA-target gene regulatory network analysis

Possible lncRNA "cis" genes are defined as chromosomal co-expression genes less than 10 kb upstream and downstream of the differentially expressed lncRNAs. In total online: https://cdn.amegroups.cn/static/public/apm-21-2046-3.xlsx shows the results of the "cis" analyses. The Basic Local Alignment Search Tool (BLAST) was used to select complementary or similar sequences of the differentially expressed lncRNAs. RNAplex was used to calculate the complementary energy between the 2 sequences to select Energy value ≤−30 sequences as trans-associated genes. In total online: https://cdn.amegroups.cn/static/public/apm-21-2046-4.xlsx shows the results of the "trans" analyses.

Construction of the ceRNA network

CeRNA analysis is a novel method for predicting the functions of lncRNAs. The miRNAs that can combine with both the differentially expressed lncRNAs and mRNAs were selected from miRBase. The ceRNA analysis provided an overview of the potential lncRNA-miRNA-mRNA interactions (*Figure 4*). The results showed that the ceRNA network was made up of 50 network nodes and 70 connections between 25 lncRNAs, 18 miRNAs, and 7 mRNAs. The mRNA showing the most connections with the lncRNAs and miRNAs in the co-expression network was CEP104. The miRNA showing the most connections

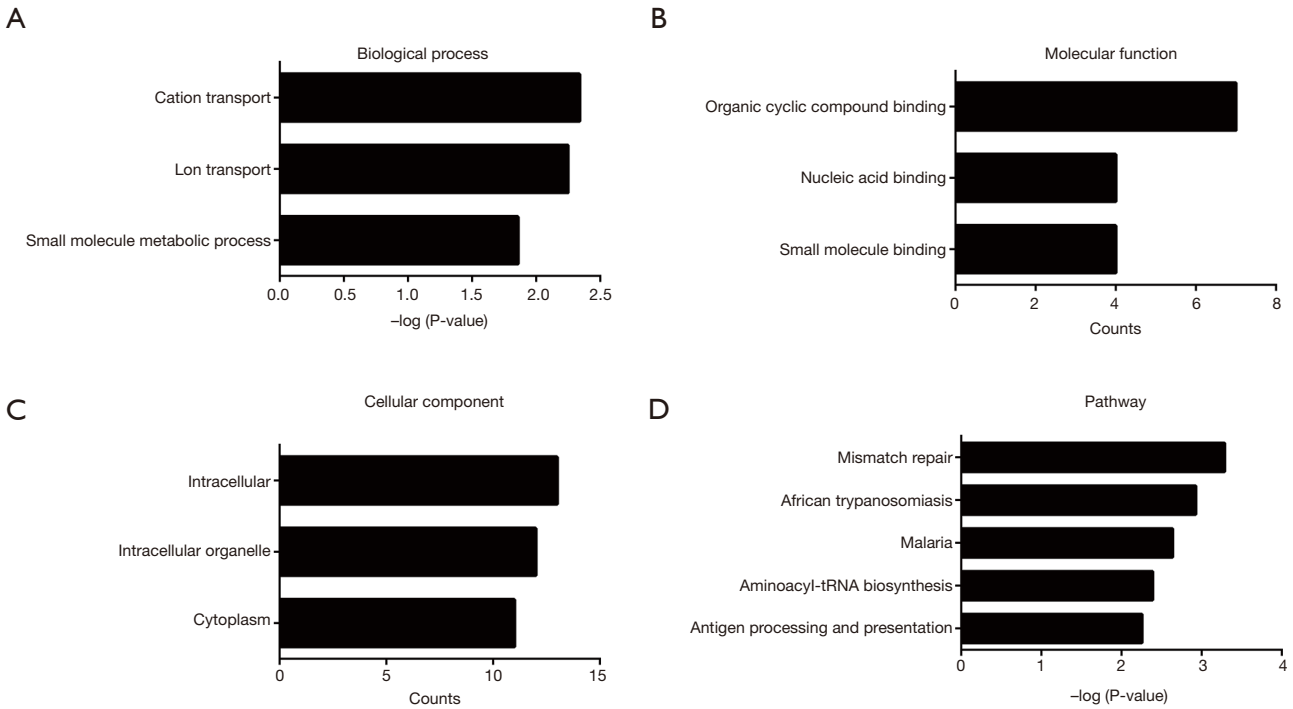

Figure 2 Gene ontology (GO) and pathway enrichment analysis for differentially regulated mRNAs. (A) The top three GO terms in the biological process. (B) The top three GO terms in the molecular function. (C) The top three GO terms in the cellular component. (D) The top five pathways of differentially expressed mRNAs in keratinocytes of patients with psoriasis vulgaris.

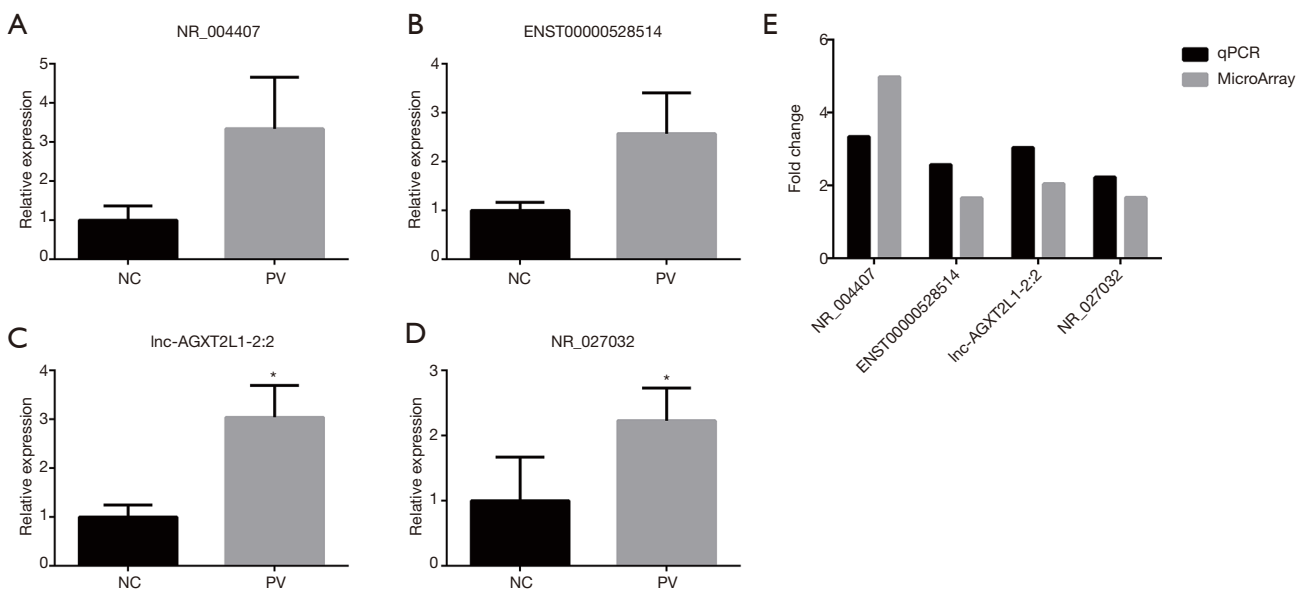

Figure 3 Confirmation of the selected long non-coding RNAs (lncRNAs) through qRT-PCR. The expression levels of (A) NR_004407 (P=0.108), (B) ENST00000528514 (P=0.083), (C) lnc-AGXT2L1-2:2 (*P=0.009), and (D) NR_027032 (*P=0.033) in keratinocytes of normal controls (NCs) and patients with psoriasis vulgaris (PV). Data is represented as mean ± standard deviation. (E) The fold change in expression obtained with microarray analysis and qRT-PCR.

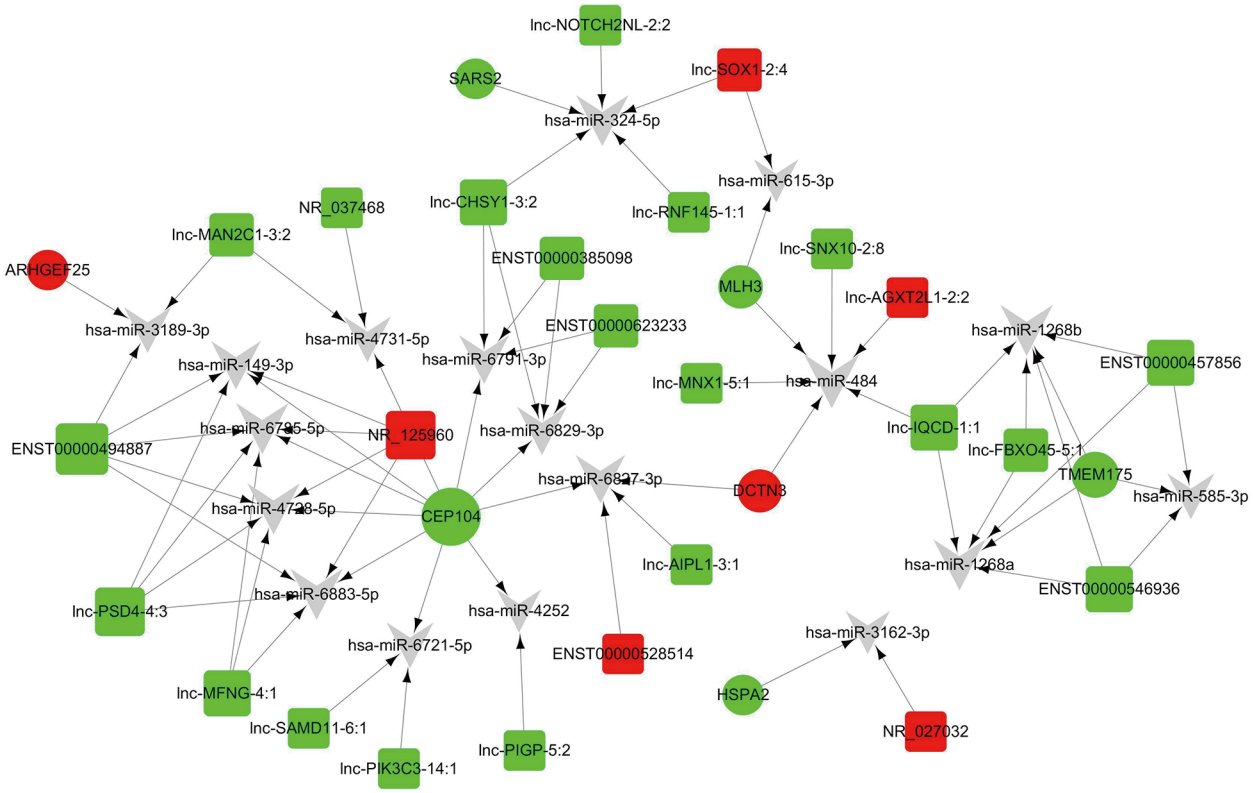

Figure 4 A ceRNA network for long non-coding RNA (lncRNA)-miRNA-mRNA in patients with psoriasis vulgaris. Triangles represent miRNAs, green circles represent down-regulated mRNAs, red circles represent up-regulated mRNAs, green squares represent down-regulated lncRNAs, and red squares represent up-regulated lncRNAs.

with the lncRNAs and mRNAs was miR-484. The lncRNA showing the most connections with miRNAs and mRNAs was ENST00000494887.

Discussion

Psoriasis is a common inflammatory skin disease that decreases the quality of life of approximately 120 million people worldwide (8). The prevalence varies between different peoples and regions. In 2017, Michalek *et al.* summarized 76 studies in more than 20 countries and regions and revealed that the incidence of psoriasis is about 0.51% to 11.43% in adults, and 0% to 1.37% in children (9). The prevalence of psoriasis in China increased from 0.12% in 1984 to 0.47% in 2012 (10), suggesting that the incidence of psoriasis in China is escalating.

The etiology and pathogenesis of psoriasis vulgaris is complex, and is yet to be fully elucidated. The disease is specific genetic susceptible and characterized by various exogenous or endogenous stimulation signals. Activation of the signaling pathway between keratinocyte growth factor (KGF) and KGF receptor (KGFR) leads to the excessive activation and proliferation of keratinocytes in psoriasis. After binding to the receptor on keratinocytes, interleukin (IL)-21 continuously activates the STAT3 pathway through the ERK pathway, while IL-22 continuously activates the STAT3 pathway through the ERK and JNK pathways, resulting in excessive or incomplete keratinization, epidermal process extension, and loss of granular layers (11,12). Keratinocytes then secrete a large number of cytokines and chemokines, including IL-17, IL-21, IL-22, interferon (IFN)-gamma and tumor necrosis factor (TNF)-alpha, which could abnormally activate T-helper (Th)1 and Th17 cells (13). The cascade amplification cross-talk between keratinocytes, T cells, dendritic cells, and other immune cells is the key factor in triggering and maintaining the pathological characteristics of psoriasis vulgaris (14). Keratinocytes can also be induced by activated T cells to produce adhesion molecules, synergistic stimulators,

other inflammatory factors (such as IL-1 and IL-6), and vascular endothelial growth factor (VEGF) which promotes angiogenesis, thereby aggravating psoriasis (15).

In addition to genetic susceptibility, environmental factors have also been associated with psoriasis vulgaris. Non-coding RNAs, including miRNAs and lncRNAs, are RNA molecules that do not encode proteins but have various biological functions. LncRNAs, with a length of more than 200 nucleoside acids, can regulate related genes at the level of chromatin modification, transcription, and post-transcriptional processing (16). LncRNAs can interact with target mRNAs by base-pairing to either increase or suppress translation in the cytosol. They can also regulate signaling pathways via RNA-protein interactions. In the nucleus, lncRNAs can interact with specific proteins to act as a guide, decoy, or scaffold (17).

To date, many studies have focused on differentially expressed lncRNAs in the blood of patients with psoriasis, but few reports have focused on lncRNAs in the epidermis of psoriasis patients, especially within the skin lesion. Tsoi *et al.* used RNA-seq data from 99 lesional psoriatic, 27 uninvolved psoriatic, and 90 normal skin biopsies to detect 2,942 previously annotated and 1,080 novel lncRNAs which are expected to be skin specific (18). Yan *et al.* identified 2,194 lncRNAs and 1,725 mRNAs that were significantly dysregulated in the skin tissue of psoriasis patients (19). However, these studies did not report on cell-specific lncRNAs within the skin. In our current study, we identified 48 lncRNAs and 17 mRNAs that were differentially expressed in skin keratinocytes of patients with psoriasis vulgaris and healthy patients. These results suggested that the imbalances in epigenetic networks may be involved in psoriasis and keratinocytes may be important regulators. Recent studies showed that lncRNAs, such as the lncRNA psoriasis-susceptibility-related RNA gene induced by stress (PRINS), can contribute to psoriasis (5). PRINS is a transcript that is highly expressed in psoriatic non-lesional epidermis and can alter the cellular stress response (20). The deregulation of PRINS may result in suppressed sensibility to spontaneous keratinocyte apoptosis under the modulation of G1P3 (5,21). However, to date, the precise roles of lncRNAs in psoriasis remain unclear.

This current investigation identified 48 lncRNAs, including lncRNA-AGXT2L1, and 17 mRNAs, including NAP1L1, that were differentially expressed in the results of the microarray. GO and KEGG pathway analyses suggested that these mRNAs were involved in cation transport, mismatch repair, and antigen processing and presentation. NAP1L1, which was part of the nucleosome assembly protein family, regulates numerous pathophysiological processes by affecting chromatin agglutination or nucleosome formation. NAP1L1 is involved in cell proliferation and differentiation (22,23), tumor development and metastasis (24), inflammation and infection (25), as well as cell proliferation. A recent study showed that lncRNA-CDKN2B-AS1 can promote NAP1L1-mediated PI3K/AKT/mTOR signaling pathway through "molecular sponge" absorption of miRNA let-7c-5p, thus leading to proliferation of liver cells (26). In our study, NAP1L1 expression was elevated in the keratinocytes of psoriasis vulgaris patients, suggesting that NAP1L1 may be involved in the proliferation of keratinocytes in psoriasis. The precise relationship between NAP1L1 and psoriasis warrants further investigation.

To verify the data of the microarrays, qPCR was performed in 15 patients and 15 healthy controls. The expression of lnc-AGXT2L1-2:2 and NR_027032 was elevated in psoriasis vulgaris patients compared to healthy controls, and this agreed with the microarray data. The expression of NR_004407 and ENST00000528514 detected by qPCR showed a similar trend to that observed with microarray analysis, however, the differences were not statistically significant. Some factors may have affected the results of the microarray. The small sample size in the microarray may lead to false positive results, and thus, the sample size was expanded in the qPCR analyses. There were also some technical limitations with the microarray, such as cross-hybridization, signal saturation, and limited dynamic range. Future studies should increase the sample size to further verify these results. To investigate the potential role of lnc-AGXT2L1-2:2 and NR_027032 in psoriasis, knockdown or overexpression experiments should be performed in the future.

Bioinformatics was used to predict complex interactions between the lncRNAs and miRNAs that were enriched in psoriasis skin lesions. ceRNAs interact with each other by competitively binding to shared miRNAs. Prediction of ceRNA cross-talk therefore relies on the identification of miRNA response elements (MREs) (27). Qiao *et al.* demonstrated that the lnc-MSX2P1-mir-6731-5p-S100A7 axis participates in the abnormal proliferation of keratinocytes in psoriasis, suggesting that the ceRNA mechanism plays a part in the regulation of psoriasis. In our ceRNA network, miR-484 was the miRNA most connected by lncRNAs and mRNAs. Previous studies have shown that miR-484 can suppress translation of mitochondrial fission

protein Fis1, and inhibit Fis1-mediated fission and apoptosis in the adrenocortical cancer cells (28). Combined with the information from the miRBase functional database, miR-484 may be closely related to the abnormal proliferation of cells. It also has co-regulatory interactions with lnc-AGXT2L1-2:2. Further investigations examining the role of the lnc-AGXT2L1-2:2- miR-484-mRNA axis in psoriasis is warranted.

Keratinocytes play important roles in skin damage in psoriasis vulgaris patients. The findings presented in this report provide insights into the hyperproliferation and hyperkeratosis of keratinocytes, and the pathogenesis of psoriasis in an epigenetic way.

Conclusions

The study demonstrated the expression profiles of lncRNAs and mRNAs in keratinocytes of patients with psoriasis vulgaris. Differentially expressed lncRNA-target gene regulatory networks and ceRNA networks were constructed. The differentially expressed lncRNAs and mRNAs may participate in the pathogenesis of psoriasis vulgaris and provide novel insights into potential treatments.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-2046). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Ethics Committee of Huashan Hospital (NO.: 2019-541) and informed consent was taken from all the patients.

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