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Original Article

Increased expression of keratin 17 in oral lichen planus and its correlation with disease severity

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KEYWORDS

Keratin 17;
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Abstract *Background/purpose:* Oral lichen planus (OLP) is a chronic inflammatory disease with unknown mechanisms of pathogenesis. Keratin 17 (KRT17) is a protein that regulates numerous cellular processes. This study aimed to explore the expression of KRT17 in OLP and its correlation with the severity of OLP.

Materials and methods: RNA sequencing using epithelium from 5 OLP patients and 5 health control (HC) was performed, followed by functional analysis. The validation cohort of 20 OLP and 20 HC tissues were used to investigate positive area value of KRT17 by immunohistochemical analysis. Reticular, erosive and ulcerative (REU) scores were used for measuring the severity of OLP.

Results: A total of 15493 genes were detected, of which 1492 genes were significantly up-regulated in OLP and 622 were down-regulated. The mRNA expression of KRT17 was elevated by 13.09-fold in OLP compared to that in HC. Pathway analysis demonstrated high KRT17 expression was associated with multiple biological processes. The median of percentage of KRT17 positive area value was 19.30 % in OLP and 0.01 % in HC ($P < 0.001$). Percentage of KRT17 positive area value was higher in erosive OLP patients (27.25 %) compared to that in

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non-erosive patients (15.02 %, $P = 0.006$). REU scores were positively correlated with percentage of KRT17 positive area value ($r = 0.628$, $P = 0.003$).

Conclusion: The mRNA expression of *KRT17* was elevated in OLP tissues compared to that in HC. KRT17 was positively correlated with the severity of OLP, indicating KRT17 might play a vital role in the pathogenesis of OLP.

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Introduction

Oral lichen planus (OLP) is a chronic inflammatory disease of the oral mucosa that as yet the mechanisms of pathogenesis are still not fully elucidated.¹ The global prevalence of OLP is 1.01 % among the general population.² As one of oral potentially malignant disorders, the malignant transformation rate of OLP is 1.4 %, ³ in which erosive OLP has a higher risk of malignant transformation than non-erosive OLP.⁴ Infiltration of T lymphocytes, disruption of the basement membrane, and degeneration of basal keratinocytes in the microenvironment have been recognized as main features of OLP.⁵

A variety of cells are involved in the immune inflammatory response of OLP, such as oral keratinocytes,⁶ which can present antigens and result in increased cytokine, chemokine and adhesion molecule expression in the pathogenesis of OLP.¹ Keratins are the typical intermediate proteins in keratinocytes and have roles in cell structure, signaling, intracellular transport, cell cycle and cell death.⁷ Altered expression of keratins has been related with oral inflammation and epithelial barrier dysfunction.^{8,9}

Among the family of keratins, we found in our previous study that only keratin 17 (KRT17) was elevated in extracellular vesicles derived from tissues from oral lichen planus,¹⁰ indicating its potential role in the pathogenesis of OLP. KRT17 belongs to the group of human type I epithelial keratins that contribute to maintaining the integrity of the epidermis.¹¹ KRT17 is a highly conserved protein and is mainly expressed in the basal cells of complex epithelia, such as in hair follicles.¹² Notably, KRT17 acts as an important factor in the pathogenesis of immune diseases.^{13,14} For instance, as an overexpressed autoantigen, KRT17 promotes the development of psoriasis, which is also a T-cell-mediated chronic inflammatory disease, through autoimmune circuits.¹⁴ Local injection of *Krt17* small interfering RNA can reduce the number of T cells in psoriasis-like dermatitis and decrease the inflammatory response.¹⁵ However, studies on KRT17 expression and its correlation with the clinical manifestations of OLP are still limited.

This study aimed to explore the expression of KRT17 in OLP and its correlation with the severity of OLP, which might provide potential targets for clinical prevention and treatment of OLP.

Materials and methods

Sample characteristics

The study was independently reviewed and approved by the Ethics Committee of Shanghai Ninth People's Hospital,

Shanghai Jiao Tong University School of Medicine (approval ID: SH9H-2019-T174-2) and conducted according to the Declaration of Helsinki and the additional requirements. Adequate understanding and written informed consent were obtained from each patient. Oral tissue samples were collected from the patients who came to the Department of Oral Medicine at Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine. The inclusion and exclusion criteria of OLP were listed in Table 1. Lesional residual tissues after biopsy were taken from OLP patients. In addition, normal oral mucosa tissue surrounding fibroma without infection in the oral cavity were collected as health control.

Acquisition of epithelial layer from OLP and HC tissues

Tissues taken from OLP and HC subjects were washed with phosphate buffered saline (PBS) containing 10 % penicillin and streptomycin solution (Gibco, Grand Island, CA, USA) for 3 times. Dispase (Roche, Basel, Switzerland) was added and kept for 10 h at 4 °C. Sterile forceps were used to carefully separate the epithelial layer, which was then cut into pieces. TRIzol reagent (Thermo Fisher Scientific, Waltham, MA, USA) was added for subsequent RNA extraction.

Table 1 The inclusion and exclusion criteria for OLP patients.

The inclusion criteria

- (1) Age 18–80 years and signed written informed consent.
- (2) Clinically diagnosed and biopsy-proven OLP according to the modified world health organization diagnostic criteria (van der Meij & van der Waal, 2003).

The exclusion criteria

- (1) Received topical or systemic treatment for OLP within 3 months.
- (2) With autoimmune diseases, such as rheumatoid arthritis, lupus erythematosus, psoriasis, Sjogren's syndrome, or autoimmune thyroiditis.
- (3) Clear oral contact lichenoid reaction, which is related to the location of the lesion and the dental restoration.
- (4) Suspected oral lichenoid drug eruptions.
- (5) With serious allergic diseases.
- (6) With serious systemic disease.
- (7) With a history of organ or bone marrow transplantation.
- (8) With infection of oral mucosa.
- (9) With mental and psychological illness.

OLP, oral lichen planus.

Construction of RNA sequencing libraries and sequencing

Total RNA was extracted from the samples by TRIzol reagent. The RNA quality was checked by Agilent 2200 and kept at -80°C . The RNA with integrity number >7.0 was acceptable for complementary DNA (cDNA) library construction. The cDNA libraries were constructed for each RNA sample using the TruSeq Stranded mRNA Library Prep Kit (Illumina, San Diego, CA, USA) according to the manufacturer's instructions. Generally, the protocol consists of the following steps: Poly-A containing mRNA was purified from $1\text{ }\mu\text{g}$ total RNA using oligo (dT) magnetic beads and fragmented into 200–600 bp using divalent cations at 85°C for 6 min. The cleaved RNA fragments were used for first- and second-strand cDNA synthesis. DUTP mix was used for second-strand cDNA synthesis, which allows for the removal of the second strand. The cDNA fragments were end repaired, A-tailed and ligated with indexed adapters. The ligated cDNA products were purified and treated with uracil DNA glycosylase to remove the second-strand cDNA. Purified first-strand cDNA was enriched by PCR to create the cDNA libraries. The libraries were quality controlled with Agilent 2200 and sequenced by NovaSeq 6000 on a 150 bp paired-end run.

RNA sequencing mapping

Before read mapping, clean reads were obtained from the raw reads by removing the adaptor sequences and low-quality reads. The clean reads were then aligned to human genome (GRCh38, Ensembl104) using the Hisat2.¹⁶ HTseq was used to get gene counts and RPKM method was used to determine the gene expression.¹⁷

Differentially expressed gene investigation

We applied DESeq2 algorithm to filter the differentially expressed genes. The thresholds for significant differential expression were set as the following criteria: (1) fold change >2 or <0.5 ; (2) $P < 0.05$.

Gene ontology (GO) and pathway analysis

GO analysis was performed to facilitate elucidating the biological implications of the differentially expressed genes in the experiment. We downloaded the GO annotations from NCBI, UniProt and the gene ontology. Pathway analysis was used to find out the significant pathway of the differentially expressed genes according to Kyoto Encyclopedia of Genes and Genomes (KEGG) database. Gene Set Enrichment analysis (GSEA) was conducted using GSEA software (version 4.1.0).

Immunohistochemistry staining of KRT17

Four-micrometer-thick histological sections were prepared from formalin-fixed paraffin embedded samples. After deparaffinization with dimethylbenzene and hydration with different concentration of ethanol, 3 % hydrogen peroxide

solution (Sinopharm, Shanghai, China) was incubated with sections at room temperature for 10 min to block the activity of endogenous peroxidase. Subsequently, sections were washed in antigen repair solution for 15 min and cooled naturally for antigen retrieval. PBS was used to wash the sections with for 3 times with 5 min each. Sections were then incubated with 5 % BSA blocking solution (Sigma, St. Louis, MO, USA) at room temperature for 20 min, followed by incubation with a 1:200 dilution of rabbit anti-human KRT17 primary antibody (Cell Signaling Technology, Danvers, MA, USA) overnight at 4°C . Wash the sections with PBS 3 times with 5 min each and remove PBS. Then, with enhance labelled polymer system antirabbit secondary antibody (DAKO, Glostrup, Denmark) incubated with sections for 30 min at 37°C . Immunolocalization of the KRT17 was detected by diaminobenzidine development, and nuclear staining was performed with hematoxylin for 30 s. Finally, sections were dehydrated with a gradient ethanol solution, the transparent reaction was performed with xylene, and the slide was sealed with neutral gum.

Semi-quantitative analysis of images of IHC

Photographs were taken for all slices under digital pathology slide scanner. Five randomly selected fields of view under high magnification in each section were used to analyze the positive area value by Image J software.

Evaluation of severity of OLP

The reticular, erosive and ulcerative (REU) scoring system was used for measuring the severity of OLP according to previous publication.¹⁸ Briefly, scores were given according to the clinical manifestations of 10 different anatomic sites, including labial mucosa, right buccal mucosa, left buccal mucosa, dorsal tongue, ventral tongue, floor of mouth, hard palate, soft palate/tonsillar pillars, maxillary and mandibular gingiva. Reticular lesions in each site scored 0 or 1; erythematous areas in each site scored from 0 to 3; ulcerative areas in each site scored from 0 to 3. REU score was calculated through the formula that $\text{REU score} = 1 \times \Sigma R + 1.5 \times \Sigma E + 2 \times \Sigma U$.

Statistical analysis

The results of continuous variables were presented in the form of means $\pm$ standard deviations. Independent t-test and Mann–Whitney U test were performed where data were of normal distribution and non-normal distribution, respectively. Chi-square or Fisher exact probability test was used for calculating the differences of clinical data of subjects. Fisher's exact test was applied to identify the significant GO categories and significant pathway. Spearman's correlation test was used to analyze the correlations between REU score and KRT17 positive area value, and results were presented as coefficient of correlation (r). SPSS 26.0 software (International Business Machines Corporation, Armonk, NY, USA) was used for data analysis. Graph Prism 9 (GraphPad Software, San Diego, CA, USA) was used for graphic figures. Possibility (P) value < 0.05 was considered statistically significant.

Results

Participant characteristics

Tissues from 5 cases of reticular OLP patients and 5 HC subjects were used for RNA-seq. Furtherly, 20 patients with OLP and 20 HC were enrolled as validation cohort using IHC staining. No significant difference was found in demographic and clinical characteristics, including age, sex, smoking, alcohol usage and lesion site, between the groups (Table 2). In the validation group, the OLP lesions in 7 patients were reticular, erythematous and erosive. Non-erosive OLP lesions were found in 13 patients, in which 8 patients were with reticular lesions alone and 5 were with both reticular and erythematous lesions.

KRT17 mRNA expression in OLP and HC by RNA-seq

The principal component analysis of RNA-seq revealed that the data were repeatable (Fig. 1A). A total of 15,493 genes were detected in two groups, of which 1492 genes were significantly up-regulated in OLP and 622 genes were significantly down-regulated (Fig. 1B–D). The average mRNA expression of *KRT17* was 106,690.8 in OLP group and 8153.6 in HC group (13.09-fold, $P = 6.54 \times 10^{-8}$).

GO and pathway analysis of *KRT17*

GO terms classification and pathway analysis of these differentially expressed genes were performed. The results of *KRT17*-associated GO terms classification indicated that the biological processes were mainly concentrated in the terms of positive regulation of hair follicle development, cornification and keratinization. The cellular components were mainly enriched in cell periphery, cytosol and cytoplasm. Molecular function was mainly characterized by structural molecule activity (Fig. 2A).

Pathway analysis revealed that KEGG pathways, in which *KRT17* might involve, included staphylococcus aureus infection (ko05150). In estrogen signaling pathway

(ko04915), *KRT17* was not statistically different between OLP and HC groups (Fig. 2B). GSEA demonstrated that high *KRT17* expression was associated with positive regulation of cell growth, positive regulation of translation, morphogenesis of an epithelium, intermediate filament organization, keratinization, cornification and hair follicle morphogenesis (Fig. 2C–I).

Immunohistochemical analysis of *KRT17*

To validate the increased expression of *KRT17* in OLP tissues, we performed IHC staining using a validation cohort. We found that *KRT17* positive cells were widely distributed throughout the epithelial layer of OLP tissue, while positive expression was rarely observed in HC tissue (Fig. 3A–F). The median of percentage of *KRT17* positive area value was 19.30 % in OLP and 0.01 % in HC (Fig. 3G, $P < 0.001$).

Association of severity of OLP and percentage of *KRT17* positive area value

We observed that percentage of *KRT17* positive area value was higher in erosive OLP patients (27.25 %, $n = 7$) compared to that in non-erosive OLP patients (15.02 %, $n = 13$, $P = 0.006$, Fig. 4A). The average REU score in 20 OLP patients was 5.10 ± 2.25 . REU scores were positively correlated with percentage of *KRT17* positive area value ($r = 0.628$, $P = 0.003$, Fig. 4B).

Discussion

In this study, RNA sequencing using oral mucosal epithelial tissue revealed that *KRT17* expression was increased in OLP tissues compared to that in HC tissues. Functional analysis indicated that *KRT17* could regulate multiple biological processes. Through a validation cohort, we found for the first time that *KRT17* was positively correlated with the severity of OLP.

In recent years, several studies have reported the results of RNA-seq using OLP tissues, but the results of *KRT17* are

Table 2 Demographic and clinical characteristics of the OLP and HC subjects.

	For RNA-seq			For immunohistochemical staining		
	OLP (n = 5)	HC (n = 5)	P-value	OLP (n = 20)	HC (n = 20)	P-value
Age at biopsy (years)						
Range	26–69	25–56		27–74	18–78	
Mean $\pm$ standard deviations	36.00 $\pm$ 18.51	35.20 $\pm$ 12.20	0.938	47.80 $\pm$ 14.90	45.40 $\pm$ 18.90	0.658
Sex						
Male	1	2	1.000	7	8	0.744
Female	4	3		13	12	
Smoking	0	0	/	1	1	1.000
Alcohol	0	0	/	1	2	1.000
Biopsy site						
Buccal/labial mucosa	3	5	0.444	14	19	0.091
Tongue	2	0		6	1	

OLP, oral lichen planus; HC, health control; RNA-seq, RNA sequencing.

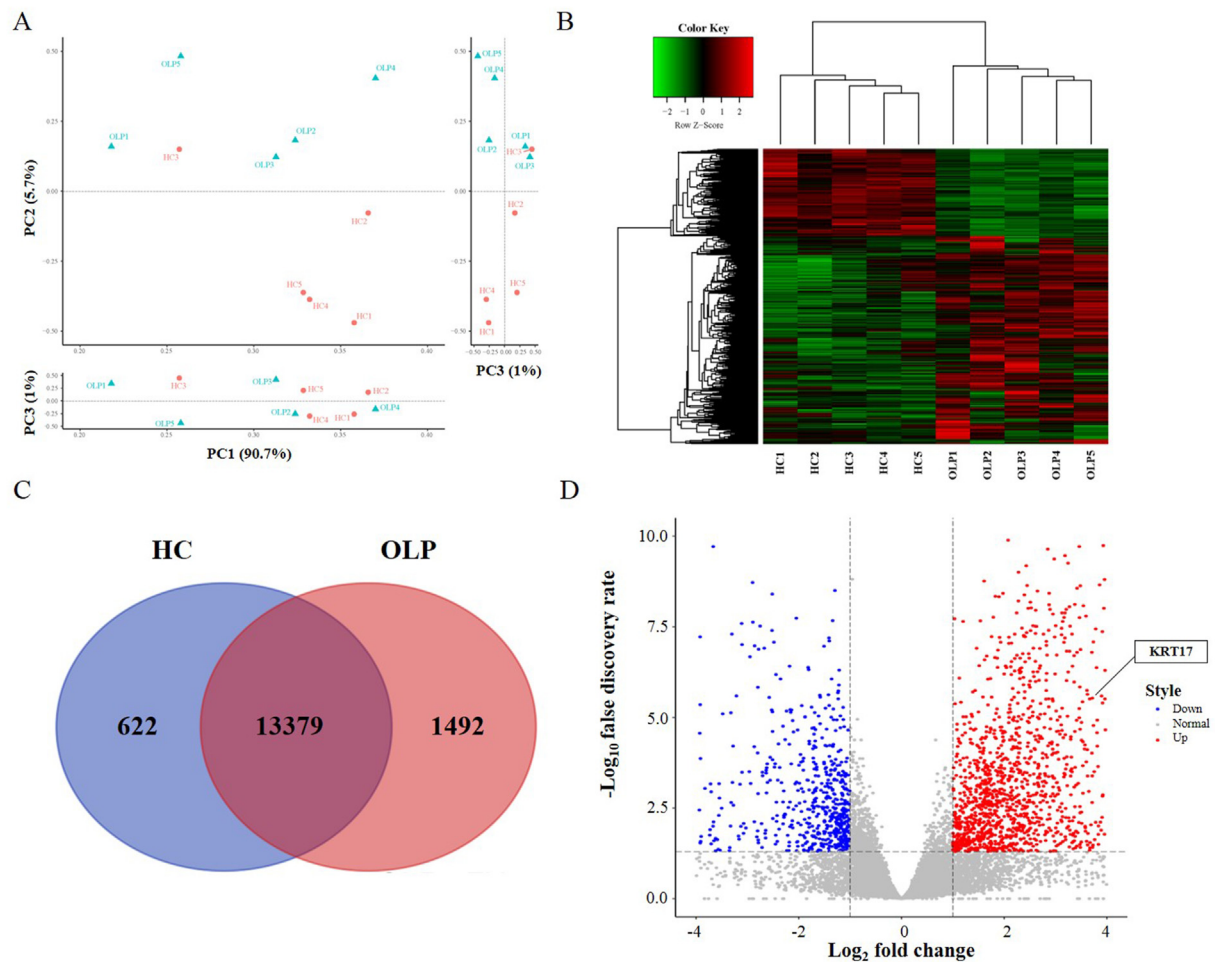


Figure 1 RNA sequencing of HC and OLP epithelium. A, principal component analysis of samples. B, cluster analysis of differentially expressed genes. C, Venn diagram. D, volcano plots. HC, healthy control. OLP, oral lichen planus.

controversial. Chen et al. performed RNA-seq analysis using 9 OLP and 4 HC tissues, and investigated 599 differentially expressed genes, in which *KRT17* expression was significantly upregulated by 2.95-fold in OLP compared to that in HC.¹⁹ Similar results were also verified by Vo et al. and de Lanna et al.,^{20,21} who analyzed the data from public databases. The results from above studies were in consistent with our result. However, Wang et al. did not find elevated *KRT17* expression using 6 OLP and 6 HC tissues.²² As for the functional analysis, we found the keratinocyte-specific biological processes such as cornification and keratinization were enriched in patients with OLP. KEGG analysis demonstrated the pathogen infection, which might be related to the impairment of epithelial barrier. The results of GSEA indicated significant enrichment of not only cornification and keratinization but also positive regulation of cell growth and translation sets in patients with OLP, confirming the possibility of a connection between epithelial barrier dysfunction and OLP.

In this study, we found for the first time that *KRT17* expression was positively correlated with REU scores, which was a widely-used objective system to evaluate the

severity of OLP.^{23,24} Through drug-response analysis and drug repositioning evaluation, de Lanna et al. recommended *KRT17* as one of the main therapeutic targets for OLP,²¹ which supported the results of this study. Similarly, *KRT17* expression and its correlation with disease severity had been reported in esophageal squamous cell carcinoma and systemic sclerosis.^{13,25} In addition, we observed *KRT17* was widely distributed in the epithelial layer, which was in accordance to the previous study.²⁶

Currently, the underlying mechanisms involving *KRT17* in the pathogenesis of OLP remain unclear. *KRT17*, together with *KRT16*, contributes to hyperproliferation and innate immune activation of keratinocytes as barrier alarmin molecules.²⁷ The absence of *Krt17* in rats leads to aberrant cell cycle progression and mitotic catastrophe in epidermal keratinocytes in skin damage,²⁸ while normal cell cycle can contribute to the development and maintenance of characteristic mucosal epithelial architectures in OLP.²⁹ In addition, *KRT17* expression is closely associated with the response to stress,¹¹ and patients with OLP suffer a higher prevalence of stress.³⁰ Our team previously found that *KRT17* might promote the development of OLP in the form

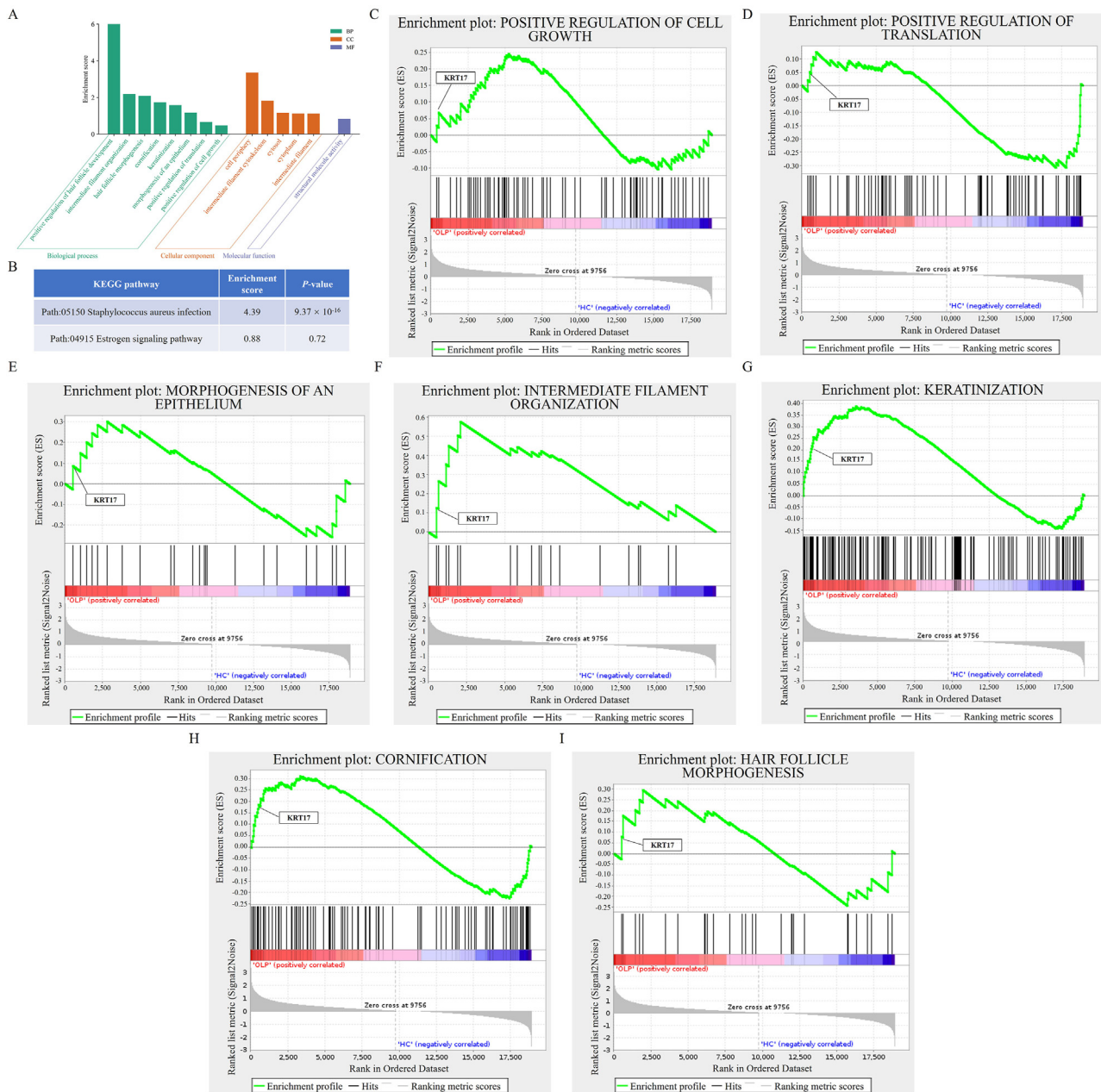


Figure 2 Predicted functions and pathways associated with *KRT17* expression in OLP. A, gene ontology analysis. B, Kyoto Encyclopedia of Genes and Genomes pathway. C – I, Gene Set Enrichment analysis. *KRT17*, keratin 17. OLP, oral lichen planus. BP, biological process. CC, cellular component. MF, molecular function.

of extracellular vesicles (unpublished data). More specific mechanisms related with *KRT17* in OLP need to be explored in future studies.

A few limitations exist for the current study. Firstly, since we focused on exploring the differential expressions in keratinocytes, dispace was used to separate the epithelial layer from the lamina propria during sample pre-processing, which might to some extent affect the results of RNA-seq. Secondly, data of subjective evaluation indicators, such as visual analogue scale, from patients with OLP in this study

were unavailable, which made us impossible to analyze the correlation between *KRT17* expression and the degree of patients' discomfort. Thirdly, we did not validate the functions of the key genes, including *KRT17*, as well as the potential signaling pathways *in vitro* or *in vivo*.

In conclusion, the mRNA expression of *KRT17* was elevated in OLP tissues compared to that in HC, and *KRT17* was positively correlated with the severity of OLP, indicating *KRT17* might play a vital role in the pathogenesis of OLP.

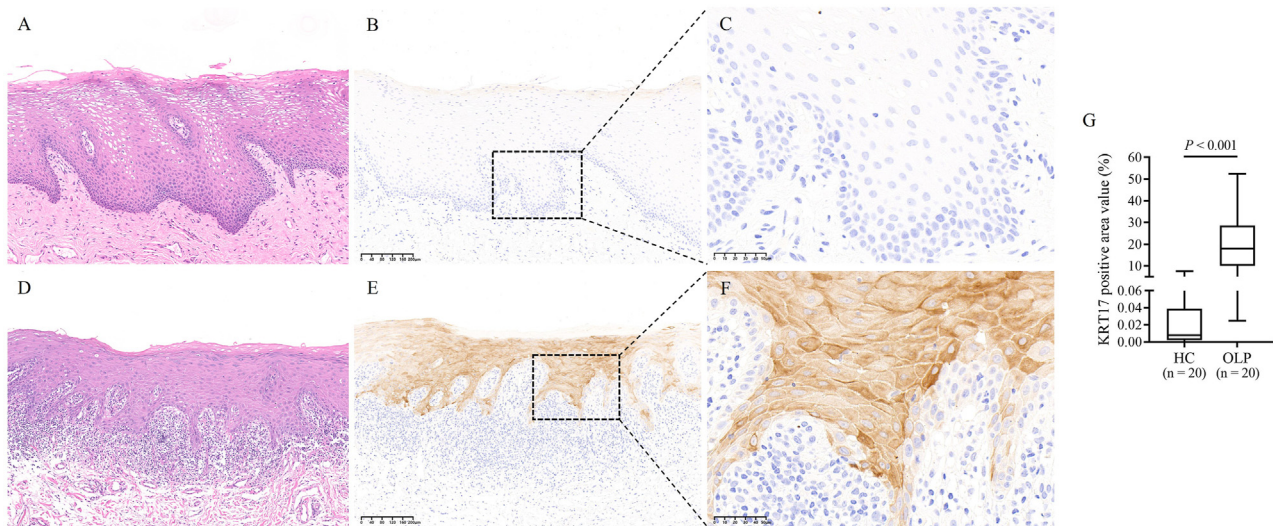


Figure 3 KRT17 expression and distribution in HC and OLP tissues. A, hematoxylin and eosin staining of HC tissue (100 $\times$). B, KRT17 immunohistochemistry of HC tissue (100 $\times$). C, KRT17 immunohistochemistry of HC tissue (400 $\times$). D, hematoxylin and eosin staining of OLP tissue (100 $\times$). E, KRT17 immunohistochemistry of OLP tissue (100 $\times$). F, KRT17 immunohistochemistry of OLP tissue (400 $\times$). G, comparison of KRT17 positive area value. KRT17, keratin 17. HC, healthy control. OLP, oral lichen planus.

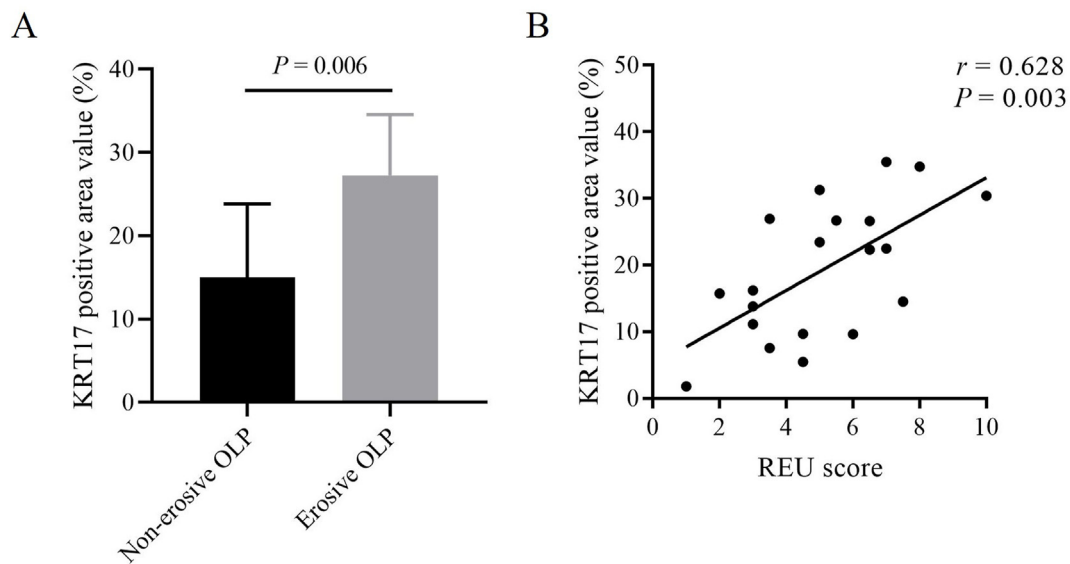


Figure 4 Correlation of severity of OLP and percentage of KRT17 positive area value. A, percentage of KRT17 positive area value in erosive and non-erosive OLP patients. B, correlation of percentage of KRT17 positive area value and REU scores. OLP, oral lichen planus. KRT17, keratin 17. REU, reticular, erosive and ulcerative.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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