Original Article

Expression profile of circular RNAs in oral lichen planus

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Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: This study sought to identify the circular RNAs (circRNAs) differentially expressed in oral lichen planus (OLP) to investigate the possible role of circRNAs in this disease's pathogenesis.

Methods: Six OLP and six normal oral mucosal tissues were used for circRNA detection and sequencing. 10 selected circRNAs were verified by reverse transcription-quantitative polymerase chain reaction (RT-qPCR). A gene ontology (GO) functional analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis were performed to predict the functions of circRNAs in OLP. TargetScan and miRanda were applied to predict targeted micro (mi)RNAs and messenger (m)RNAs of circRNAs, and competing endogenous (ce)RNA networks were mapped.

Results: One hundred and thirty-five circRNAs were identified differentially expressed in OLP tissues compared to normal control tissues, including 83 upregulated circRNAs, and 52 down-regulated circRNAs. RT-qPCR confirmed that 10 circRNAs were all abnormally expressed in OLP. The GO functional analysis and KEGG pathway analysis showed that differentially expressed circRNAs were involved in 535 GO functional items and 78 signal pathways. A ceRNA network analysis showed that circRNAs might interact with a variety of miRNAs.

Conclusions: This study mapped the expression profile of abnormally expressed circRNAs in OLP tissues for the first time and showed that circRNAs appear to play an important role in the pathogenesis of OLP.

Keywords: Circular RNA (circRNA); oral lichen planus (OLP); high-throughput sequencing; ceRNA; miRNA

Submitted Nov 12, 2020. Accepted for publication Mar 31, 2021.
doi: 10.21037/apm-20-2253
View this article at: http://dx.doi.org/10.21037/apm-20-2253

Introduction

Oral lichen planus (OLP) is a common chronic inflammatory disease that affects the skin, genitalia, and oral mucous membrane. The prevalence of OLP is 1–2% (1), and it often occurs in middle-aged people, especially women (2). Most OLP patients suffer pain or other uncomfortable sensations when the lesioned areas are touched (3). The etiology and pathogenesis of OLP remain unclear, but many studies have reported that it is a T-lymphocyte-mediated autoimmune disease (4). The probability of OLP transforming into oral squamous cell carcinoma is about 1–2% (5). OLP has been classified as a potentially malignant disorder by the World Health Organization. Thus, the prevention and early treatment of OLP have considerable clinical significance.

Circular RNA (circRNA) is a popular new area of RNA

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Table 1 The clinical characteristics of patients for sequencing

Number	Age (yr)	Gender (M/F)	Location	Type
P1	37	F	Buccal	Reticulated
P2	36	F	Ventral of the tongue	Reticulated
P3	29	F	Dorsal of the tongue	Reticulated
P4	65	M	Dorsal of the tongue	Reticulated
P5	38	M	Dorsal of the tongue	Reticulated
P6	34	M	Ventral of the tongue	Reticulated
N0	17	F	Buccal	
N1	33	F	Buccal	
N2	27	F	Buccal	
N3	23	M	Buccal	
N4	23	F	Buccal	
N5	25	M	Buccal	

research. CircRNA is produced by the back splicing of precursor messenger RNA in eukaryotes (6). CircRNAs are expressed in cell-type and tissue-type specific patterns and occur widely in eukaryotes (6-8). Unlike linear RNAs, circRNAs have no 5' cap structure or 3' adenylate tail. Further, as they cannot be broken down by ribonuclease, which is an exonuclease enzyme that degrades linear RNA molecules, they are more stable than linear RNAs (6). Most circRNAs are exonic; however, intronic circRNAs, intergenic circRNAs, antisense circRNAs, or sense overlapping circRNAs also exist (9,10).

Since Hansen *et al.* (11) first published a paper on the function of circRNA in the *Nature* journal in 2013, an increasing number of studies have shown that circRNAs play important roles in the pathogenesis of diseases and are potential molecular markers (12,13). By binding micro (mi) RNA through miRNA response elements, circRNAs act as "miRNA sponges" to undermine the inhibitory effects of miRNAs on their target mRNAs and thus regulate the expression level of mRNAs (14-16). The expression of circRNAs in the process of immune response and immune-related diseases can be altered (17). Additionally, circRNAs can promote immune responses and affect the process of autoimmune diseases, tumor immunity, and antiviral immunity (18).

Thus, circRNAs play important roles in regulating gene expression and participating in the pathogenesis of many diseases. However, the expression profile of circRNAs in OLP has not yet been determined. This study sought to identify the circRNAs differentially expressed in OLP to investigate the possible role of circRNAs in this disease's occurrence and development.

We present the following article in accordance with the MDAR checklist (available at http://dx.doi.org/10.21037/apm-20-2253).

Methods

Patients and samples

Biopsies of oral mucosa were collected from 6 OLP patients who were clinically and pathologically diagnosed with OLP at the Department of Oral Mucosa, The Ninth People's Hospital of Shanghai, Jiaotong University, School of Medicine (Shanghai, China) between September and October 2018. Six normal oral mucosae samples (without inflammation) were collected as controls samples from patients who underwent plastic surgery in the Plastic Surgery Department (see *Table 1*). All of the samples were stored at −80 ℃ until RNA extraction. None of the patients had used local or systemic glucocorticoids or had suffered from severe cardiovascular system disease or any liver, kidney, or other organ dysfunction. All of the patients participated voluntarily in this study and signed informed consent forms before the surgery. The study was approved by the Ethics Committee of The Ninth People's Hospital of Shanghai [No. 89 (2012) 21]. The study was conducted in accordance with the Declaration

Table 2 Ten selected circRNAs and the primers for RT-qPCR experiments

circRNA ID	Primer type	Primer sequence (5'-3')
chr6:31238920-31324013-	Forward	CGGCAAGGATTACATCGC
	Reverse	CCTTCCCGTTCTCCAGGT
hsa_circ_0060927	Forward	GGCCACAGACAATGAGCC
	Reverse	AAATCGGCCAAGACCTCA
hsa_circ_0008776	Forward	CCCTGGGAGAGAGGAGGA
	Reverse	GTGCTACATGGCCTGGCT
chr19:4511523-4511918-	Forward	TGTGTGCAGTGGGGTGAC
	Reverse	CCCTTTGGCGACATTCAC
hsa_circ_0117628	Forward	TCCGGGAGAACCAAAAGA
	Reverse	TCCAGTTCCAGGTCTCGC
hsa_circ_0000727	Forward	CCTGCTCTGGGACACACC
	Reverse	TTCACCGACAAATCCCGT
hsa_circ_0004494	Forward	TGCTCTCCTTGCACCTGA
	Reverse	TGGCATATTTGGCTTGACG
hsa_circ_0003943	Forward	ACCACCTCCCTTTTCCCA
	Reverse	CATGCTGTAGCACTGCCG
hsa_circ_0066251	Forward	GGACATCAAGCGGGAGAA
	Reverse	GCATCATGGTCTGGTGTTG
hsa_circ_0006867	Forward	CCTTGCCCACCAACTTCA
	Reverse	AGCCATTTTCCATGCAGC

of Helsinki (as revised in 2013).

RNA isolation and quality control

Trizol (Life Technologies, Carlsbad, CA, USA) isolated total RNA from the OLP and normal oral mucosal tissues. The NanoDrop ND-1000 (Thermo Fisher Scientific, Waltham, MA, USA) was used to determine the purity and quantity of the isolated total RNA. The spectrophotometer OD260/OD280 value was used as the RNA purity index; an OD260/OD280 value between 1.8 and 2.1 was set as the range for qualification.

RNA library construction and circRNA sequencing analysis

CloudSeq Biotech (Shanghai, China) undertook the RNA library preparation and high-throughput sequencing. Ribo-Zero rRNA Removal Kits (Illumina, USA) were used to remove ribosomal (r)RNA from total RNA for each sample. The TruSeq Stranded Total RNA Library Prep Kit (Illumina, USA) was used to construct RNA libraries for the rRNA-depleted RNAs. The BioAnalyzer 2100 system (Agilent Technologies, USA) was used to conduct quality control and quantify the sequencing libraries. A gene ontology (GO) functional analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis were performed to predict the functions of the circRNAs.

Reverse transcription-quantitative polymerase chain reaction (RT-qPCR)

As *Table 2* shows, 10 circRNAs with significant differences were selected from the sequencing results. The selection criteria were a large logFC value, a small P-value, and an average original signal expression value. RT-qPCR

verification was performed on the 12 samples. RT-qPCR verification was performed on these 12 samples. The qPCR SYBR Green master mix (Cloudseq, Shanghai, China) was used to undertake the RT-qPCR of the 10 selected circRNAs. The RNase Inhibitor (Enzymatics, Green Bay, WI, USA), SuperScript^{TM} III Reverse Transcriptase (Thermo Fisher Scientific, Chino, CA, USA), and dNTP Mix (HyTest Ltd., Turku, Finland) were used to construct complementary deoxyribonucleic acid (cDNA) libraries. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used as an endogenous reference gene. The data analysis was performed using the $2^{-\Delta\Delta CT}$ method.

Functional enrichment analysis and ceRNA network analysis

A GO functional analysis and a KEGG pathway analysis were performed on the host genes of abnormally expressed circRNAs to predict these circRNAs' function and identify the possible pathways involved. The GO analysis mainly examined the biological processes, cellular components, and molecular functions of the circRNAs. TargetScan and miRanda were used to predict the target miRNA of abnormally expressed circRNAs, and Cytoscape (v2.8.0) software was used to construct a ceRNA network map.

Statistical analysis

Graphpad Prism version 8.0 and statistical software SPSS 19.0 (SPSS, Chicago, IL, USA) was used for the statistical analysis. The quantitative data were expressed as mean ± standard deviation (SD). Unpaired *t*-tests analyzed differences between the two groups.

Expression profile and characteristics of differentially expressed circRNAs between OLP and normal oral mucosal tissues

Six oral mucosal tissues from untreated patients with OLP and 6 normal oral mucosal tissues were used for the circRNA sequencing; 21,505 circRNA transcripts were identified, of which 15,801 were upregulated, and 5,704 were downregulated in OLP; 135 circRNAs were identified (with fold changes ≥2.0 and a P<0.05) as differentially expressed circRNAs. Eighty-three circRNAs were significantly upregulated, and 52 were markedly downregulated. A volcano plot (see *Figure 1A*), a scatter plot (see *Figure 1B*), and a hierarchical clustering heatmap (see *Figure 1C*) showed that the expression levels of the circRNAs differed significantly between the OLP group and normal oral mucosal group.

The original sequencing data have been uploaded to the GEO website (https://www.ncbi.nlm.nih.gov/geo/); the GEO serial number is GSE131567.

Among the 135 differentially expressed circRNAs, 19 were identified for the first time and deemed novel circRNAs; the remaining 116 circRNAs had been reported previously in published circRNA databases or articles (see *Figure 2A*). These circRNAs were located across all human chromosomes, except the Y chromosome. No circRNA located across the mitochondrial genome was found (see *Figure 2B*). In terms of length, 116 identified circRNAs were less than 2,000 nucleotides (nt), and 19 were more than 2,000 nt (see *Figure 2C*). Among the 135 identified circRNAs, 113 were exonic circRNAs, 8 were intronic circRNAs, 13 were overlapping circRNAs, and 1 was an intergenic circRNA (see *Figure 2D*).

Results of RT-qPCR

Seven upregulated and three downregulated circRNAs were screened according to their fold changes and P values between the OLP and normal oral mucosal samples. These 10 significantly differentially expressed circRNAs were confirmed by RT-qPCR, and all of them showed the same significant differences as those detected in the sequencing results (see *Figure 3*). Chr19:4511523-4511918-, hsa_circ_0004494, chr6:31238920-31324013-, hsa_circ_0060927, hsa_circ_0008776, hsa_circ_0117628, and hsa_circ_0000727 were upregulated and hsa_circ_0006867, hsa_circ_0003943, and hsa_circ_0066251 were downregulated. Among these 10 circRNAs, chr19:4511523-4511918-, and chr6:31238920-31324013- were novel circRNAs. The biological features of these 10 circRNAs are set out in *Table 3*.

Predicted GO function and KEGG functional pathways of circRNAs in OLP

The GO enrichment analysis predicted that the target host genes' functions were involved in biological processes, cellular components, and molecular functions. A total of 535 GO functional items were enriched. *Figure 4* shows the top 10 annotation terms under which the differentially expressed circRNAs are clustered. Differentially expressed circRNAs are mainly involved in biological processes (e.g., "antigen processing and [the] presentation of

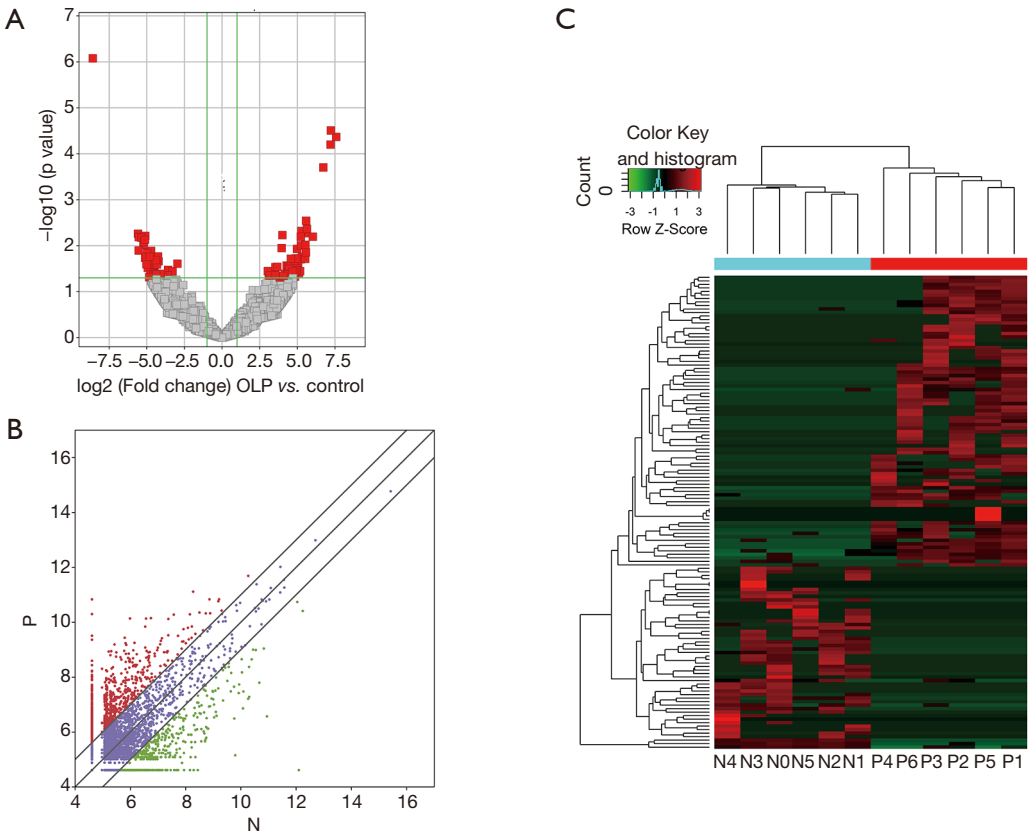

Figure 1 Expression profiles of circRNAs in OLP and normal oral mucosal tissues. (A) The volcano plots show the differential expression of circRNAs between oral lichen planus (OLP) and normal oral mucosa. The vertical line shows 2-fold (log_2 scaled) up or down changes; the horizontal line represents a P value of 0.05 (log_{10} scaled). The red spots indicate the differentially expressed circRNAs with statistical significance. (B) A scatter plot of circRNA expressions in OLP and normal tissues. The X and Y axes represent the averages of normalized signal values in different groups (log_2 scaled). Red: upregulated circRNAs with $log_{FC} \geq 2.0$; green: downregulated circRNAs with $log_{FC} \leq 2.0$. (C) A clustered heatmap; each column represents a sample, and each row represents a circRNA identified by circRNA sequencing. The red indicates upregulated circRNAs, and the green indicates down-regulated circRNAs. N, normal oral mucosal tissues; P, oral mucosal biopsies from OLP patients.

endogenous peptide antigen[s]," the "positive regulation of macroautophagy," and "antigen processing and [the] presentation of endogenous antigen[s]"), participated in the composition of cellular components (e.g., the "MHC class I protein complex"), and were involved in molecular functions (e.g., "ubiquitin-like modifier activating enzyme activity").

The KEGG analysis results revealed the pathways related to the functions of the target genes of the differentially expressed circRNAs (see *Figure 5*). A total of 78 signal pathways were identified, of which 75 were involved in upregulated genes, and 7 were involved in downregulated genes. Among these, 4 were enriched in both upregulated and downregulated genes, including the "Phospholipase D signaling pathway," "ErbB signaling pathway," "Ras signaling pathway," and "Pathways in cancer." *Figure 6* shows the detailed pathway signals of the "B-cell receptor signaling pathway," "T-cell receptor signaling pathway," "cGMP-PKG signaling pathway," and "phospholipase D signaling pathway."

Prediction and visualization of a ceRNA network

The downstream miRNAs of the 10 circRNAs verified by RT-qPCR were predicted, and a ceRNA network map was constructed (see *Figure* 7). The results showed that

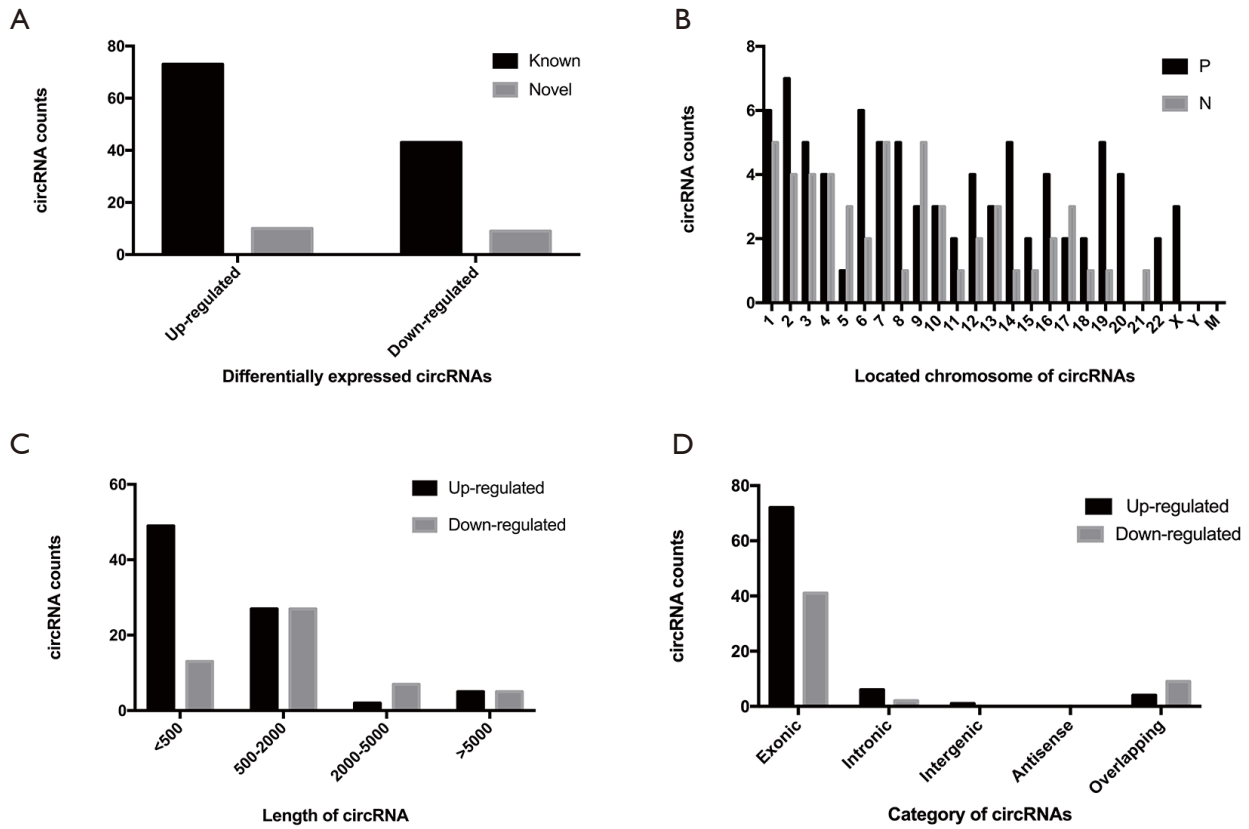

Figure 2 Distribution of characteristics of significantly dysregulated circRNAs. (A) 135 circRNAs showed significant differential expression with over 2-fold change ($P<0.05$) in the OLP group compared to the normal group, 19 novel circRNAs were identified (gray), and 116 were found in the circBase (black). (B) The distribution of differentially expressed circRNAs is based on locations on human chromosomes. (C) The distribution of the differentially expressed circRNAs based on the length of the nuclear acids. (D) The counts of differentially expressed circRNAs are based on their categories of circle components. OLP, oral lichen planus.

10 selected circRNAs all had miRNA response elements, and may bind with miRNAs; for example: chr6:31238920-31324013-, hsa_circ_0006867, hsa_circ_0066251 may bind with hsa-miR-27b-3p, Chr6:31238920-31324013- may bind with hsa-miR-802, chr6:31238920-31324013-, and hsa_circ_0060927 may bind with hsa-miR-137.

Discussion

As stated above, OLP is a common chronic inflammatory disease of the oral mucosa. In addition to the etiology and pathogenesis of OLP being complex and unknown, there is a lack of clinically effective drugs to treat OLP (2,3). Thus, the pathogenesis of OLP needs to be studied, and effective therapeutic targets for the prevention and treatment of this disease need to be found.

CircRNAs can act as miRNA sponges to abolish the inhibitory effects of miRNAs on their target mRNAs, thus increasing the expression levels of mRNAs (14-16). In recent years, it has been confirmed that circRNAs play important roles in the pathogenesis of diseases and are potential molecular markers (12,13). Thus, it is extremely important to study the role of circRNAs to aid in the diagnosis and treatment of OLP. However, a review of the literature revealed that no studies of circRNAs in OLP appear to have been conducted to date.

The present study showed that there were large numbers of abnormally expressed circRNAs in OLP, including 83 upregulated and 52 downregulated circRNAs. The RT-qPCR results were consistent with the sequencing results (i.e., the results confirmed that the selected 10 circRNAs were abnormally expressed in OLP and provided further evidence of the sequencing data's reliability). Among these 135 differentially expressed circRNAs, 19 were novel

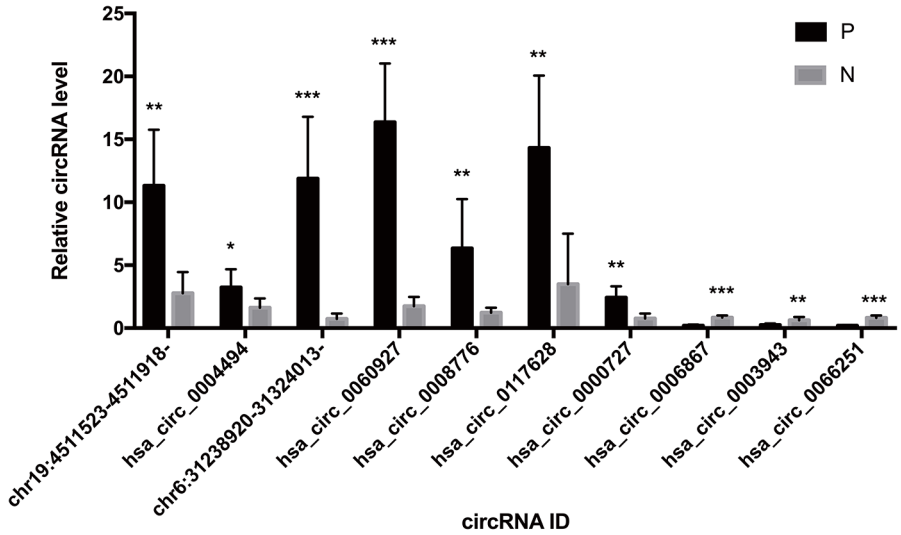

Figure 3 The relative levels of the 10 circRNAs according to the RT-qPCR. The levels of circRNAs from RNA sequencing were expressed as the fold-change ratio of the OLP group to the normal group (log 2 transformed) for each circRNA. N, normal oral mucosal tissues; P, oral mucosal biopsies from OLP patients. *, P<0.05; **, P<0.01; ***, P<0.001. OLP, oral lichen planus.

Table 3 The biological features of the ten circRNAs validated by real-time qPCR

circRNA ID	Gene name	CircBase ID	logFC	P value	Category	Length
chr6:31238920-31324013-	*HLA-C*	novel	7.229402	0.0000312365	Sense overlapping	85,094
chr20:52773708-52788209-	*CYP24A1*	hsa_circ_0060927	6.727288	0.00019872	Exonic	1,106
chr13:52971367-52972329-	*THSD1*	hsa_circ_0008776	5.641473	0.004319603	Exonic	963
chr19:4511523-4511918-	*GSE61474_ XLOC_031263*	novel	5.588909	0.002874637	Intronic	396
chr2:152363423-152370942-	*NEB*	hsa_circ_0117628	5.246577	0.009827886	Exonic	540
chr16:89484692-89497734-	*ANKRD11*	hsa_circ_0000727	5.23565	0.01978105	Exonic	156
chr13:33306238-33309467+	*PDS5B*	hsa_circ_0004494	4.176556	0.041078171	Exonic	283
chr7:6854395-6862991-	*CCZ1B*	hsa_circ_0003943	–4.66842	0.017144	Exonic	390
chr3:57276884-57301820+	*APPL1*	hsa_circ_0066251	–5.52918	0.006518	Exonic	1,478
chr4:151388825-151412187-	*LRBA*	hsa_circ_0006867	–5.57756	0.005513	Exonic	450

circRNAs. Of these 19, chr6:31238920-31324013- and chr19:4511523-4511918- were verified by RT-qPCR, and both were significantly upregulated in OLP. The host gene of chr6:31238920-31324013- was *HLA-C*, which plays an important role in the human immune system. The high cell-surface expression of HLA-C was related to aggravating cytotoxic T-cell responses (19). Hsa_circ_0006867 was downregulated in OLP and was derived from *LRBA*. LRBA participates in the regulation of the secretion and membrane deposition of immune effector molecules. A lack of LRBA leads to defects in regulatory T cells, which caused immune disorders (20). As is well known, OLP is a T-cell-mediated autoimmune disease (21,22). The abnormal expression of chr6:31238920-31324013- and hsa_circ_0006867 in OLP suggests that they may be involved in the T-cell-mediated immune process OLP. Also, this study showed that hsa_

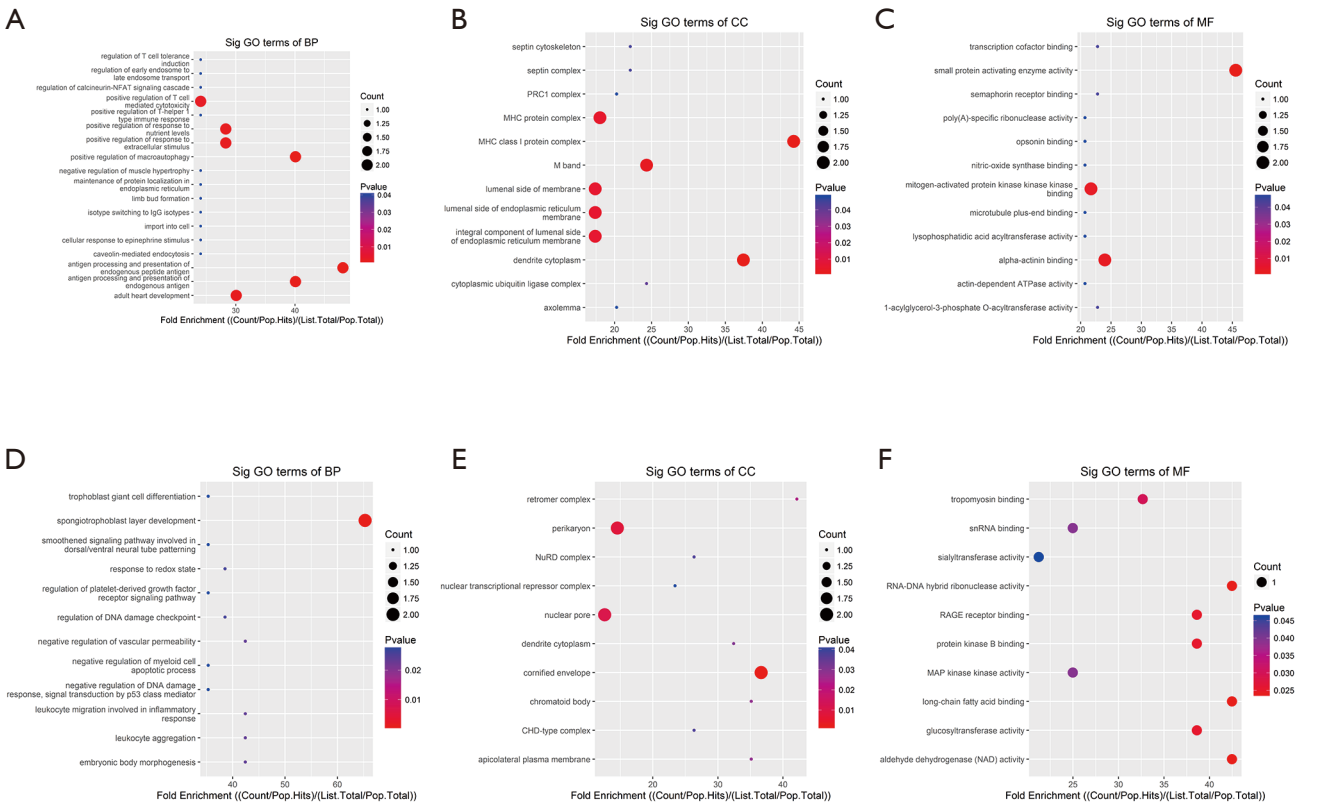

Figure 4 CircRNAs from GO function analysis. The results of the GO function analysis to identify (A) the biological process of the upregulated circRNAs; (B) the cell components of the upregulated circRNAs; (C) the molecular functions of the upregulated circRNAs; (D) the biological processes of the downregulated circRNAs; (E) the cell components of the downregulated circRNAs; and (F) the molecular functions of the down-regulated circRNAs. GO, gene ontology.

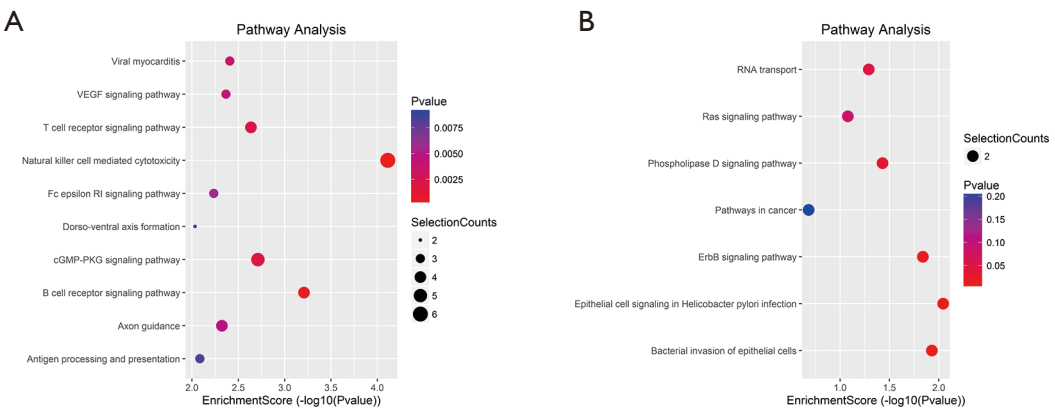

Figure 5 KEGG signal pathways related to differentially expressed circRNAs. (A) The top 10 KEGG pathways involved in upregulated circRNAs. (B) The 7 KEGG pathways involved in downregulated circRNAs. KEGG, Kyoto Encyclopedia of Genes and Genomes.

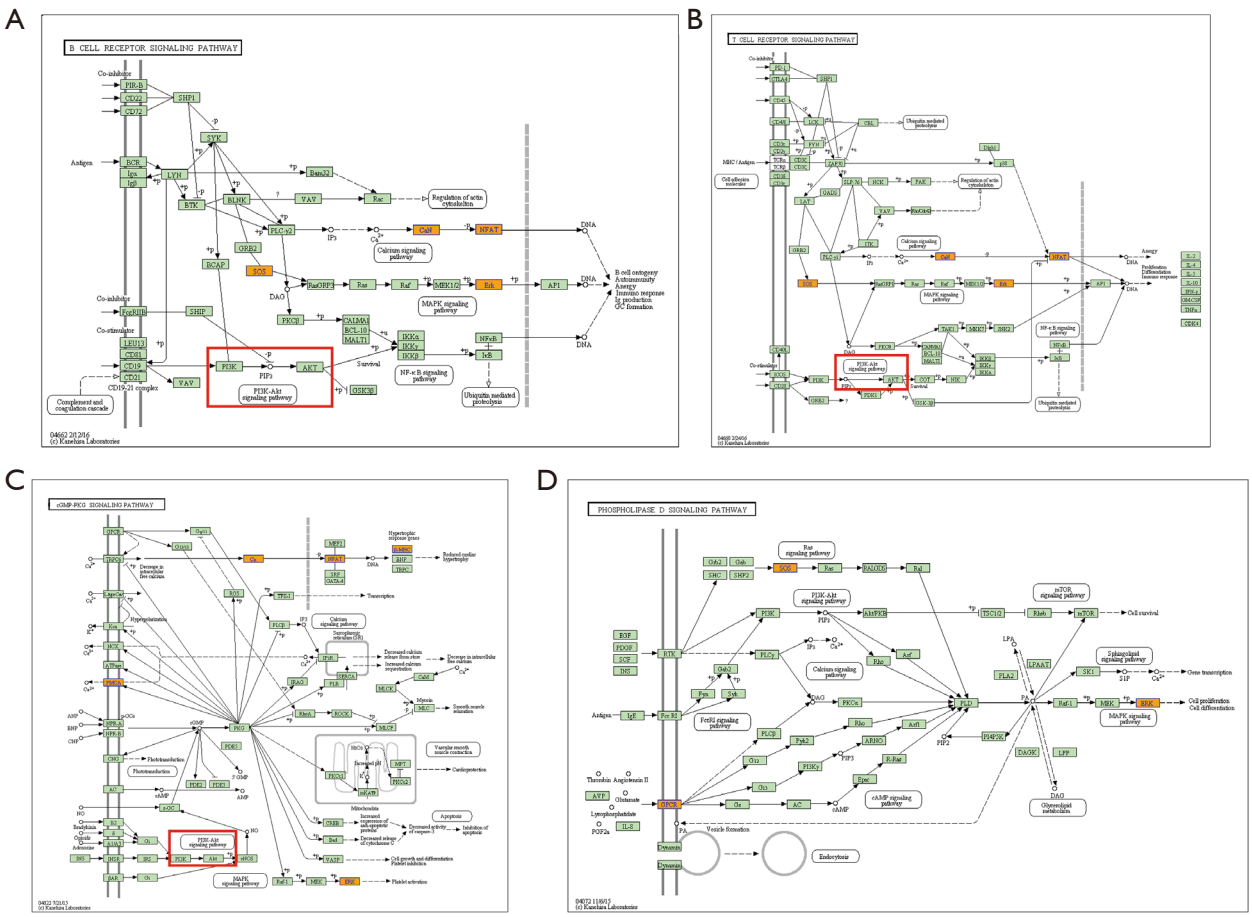

Figure 6 KEGG signal pathways related to differentially expressed circRNAs in patients with OLP. (A) B-cell receptor signaling pathway. (B) T-cell receptor signaling pathway. (C) cGMP-PKG signaling pathway. (D) phospholipase D signaling pathway. KEGG, Kyoto Encyclopedia of Genes and Genomes; OLP, oral lichen planus.

circ_0060927 was significantly upregulated. Its parental gene was *CYP24A1*, which encodes the protein CYP24A1. CYP24A1 is a mitochondrial enzyme, the main enzyme responsible for the degradation of active vitamin D, and has an important association with cancer (23,24). It has been reported that hsa_circ_0060927 is also abnormally expressed in uterine leiomyomas and colorectal cancer (25,26). The polymorphism of the *CYP24A1* gene has been associated with the risk of OLP (27). Research has also shown that after *CYP24A1* knockout, oral epithelial cells can regulate antibacterial activity by expressing higher levels of VDR-mediated (Vitamin D receptor mediated) genes (28). However, the question as to whether hsa_circ_0060927 plays a role in the occurrence of OLP needs to be addressed.

The GO enrichment analysis showed that the identified circRNAs were involved in 382 biological processes, 99 cellular components, and 54 molecular functions. According to fold enrichment ranking, 7 of the top 10 biological processes were related to immunity, such as "antigen processing and [the] presentation of endogenous peptide antigen[s]," the "positive regulation of macroautophagy," and "antigen processing and [the] presentation of endogenous antigen[s]." Thus, it appears that circRNAs may be involved in the immunological process of OLP. The cell component item with the highest fold enrichment was the "MHC class I protein complex." MHC I participates in recognition of T cells by binding to T-cell antigen receptors (29). Among 54 molecular function items, the most enriched was the "ubiquitin-like modifier activating enzyme activity." Ubiquitin-like protein has been shown to play an important role in the process of protein folding (30). It is also involved in DNA damage responses, cell cycle control, cell signal transduction, protein transport, and an

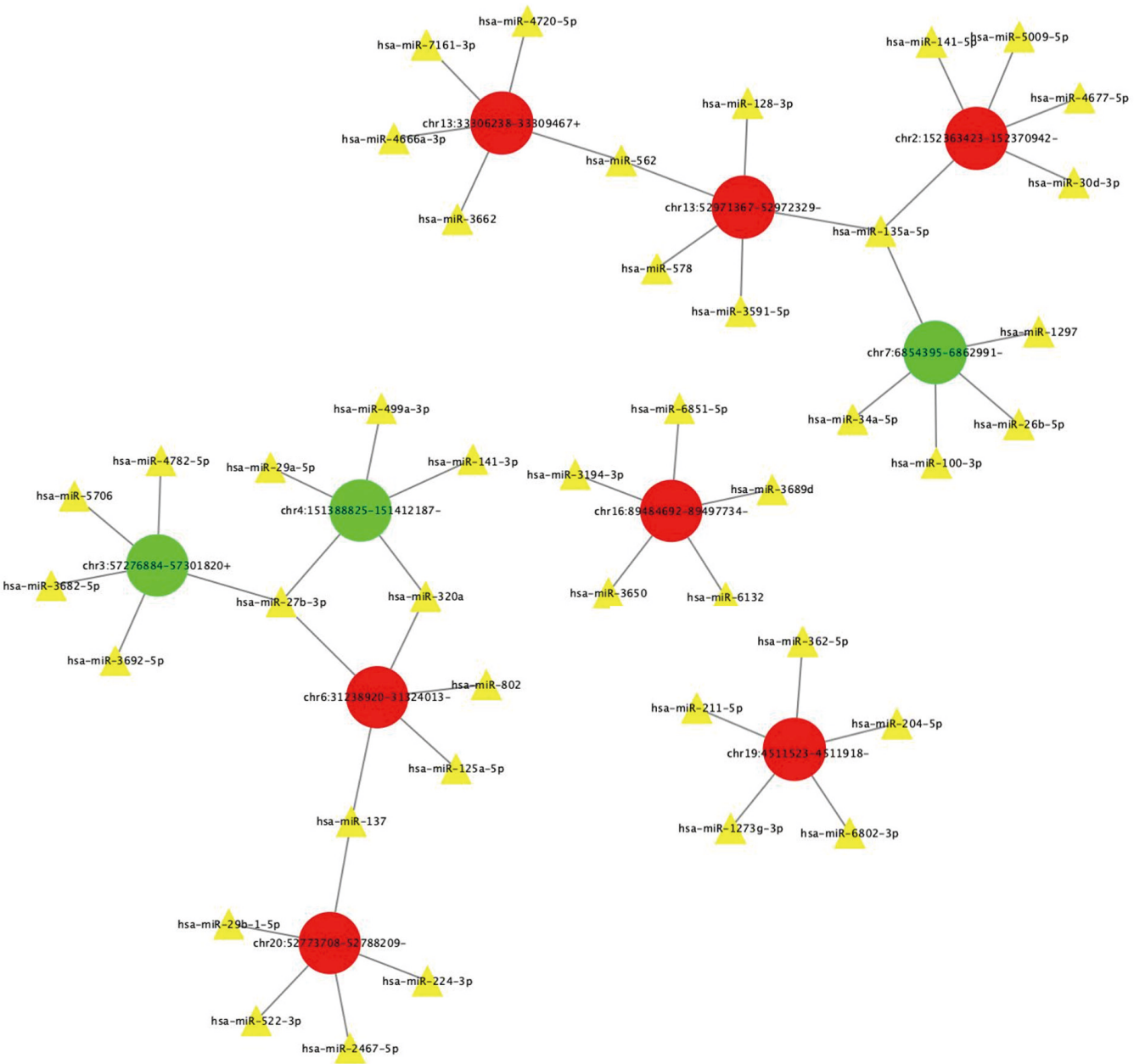

Figure 7 ceRNA network. The relationship between 10 circRNAs verified by RT-qPCR, and the targets miRNAs.

innate immune activation process (30,31). To date, no research related to ubiquitin in the field of OLP appears to have been conducted. The significant enrichment of the "ubiquitin-like modifier activating enzyme activity" suggests that it may play an important role in OLP. The GO function items enriched in this study indicate that circRNAs have various functions and may play a role in the occurrence of OLP.

The KEGG pathway analysis was performed to infer the function of circRNA by analyzing the pathway involving in circRNA-derived genes. Among 78 signal pathways that were enriched, the pathway with the highest enrichment score was the "natural killer cell-mediated cytotoxicity" pathway. Natural killer cells infiltrated the OLP tissues (32). CircRNAs may affect the occurrence of OLP by participating in the regulation of natural killer cell-mediated cytotoxicity. The enrichment scores ranked second to fourth were the "B-cell receptor

signaling pathway," the "cGMP-PKG signaling pathway," and the "T-cell receptor signaling pathway." These pathways all contained PI3K/AKT signals. The PI3K/AKT signal was abnormal in OLP, which participated in the immune regulation mechanism of OLP by regulating the crosstalk between the T cells and keratinocytes (33). CircRNAs may also participate in the immune regulation of OLP by regulating PI3K/AKT signaling. The "phospholipase D (PLD) signaling pathway" was enriched in both the upregulated and downregulated genes. Wang *et al.* (34) reported that the PLD2/MTOR/HIF-1α signal might play an important role in immune dysfunction in OLP patients. It has also been reported that PLD2 is highly expressed in OLP, and PLD2 promotes T-cell proliferation and pro-inflammatory phenotype differentiation in OLP (35).

Additionally, 6 immune-related signal pathways were enriched, which suggests that abnormally expressed circRNAs may be involved in regulating the immune process. We also enriched signal pathways related to viral infections and endocrine diseases and found that viral infection and endocrine factors may play a role in the occurrence of OLP. The pathways enriched by the KEGG analysis are of great significance to OLP's occurrence and provide a theoretical basis for future research on the pathogenesis of OLP.

TargetScan and MiRanda software were used to predict the miRNA downstream of circRNAs. A ceRNA network diagram showed that abnormally expressed circRNAs in OLP might interact with a variety of miRNAs. Previous studies have shown that (36) that miR-27b-3p inhibited oral keratinocyte apoptosis by targeting CypD/Bcl-2 signaling in OLP, while miR-802 suppressed oral keratinocyte apoptosis by targeting Bcl-2 (37). We observed an interesting phenomenon, that is, that chr6:31238920-31324013- may interact with miR-27b-3p and miR-802 simultaneously. We also found that hsa_circ_0060927 may interact with miR-137. Notably, miR-137 is significantly downregulated in OLP, and an inverse correlation between miR-137 and CD8 has been found (38,39). Hsa_circ_0003943 may interact with miR-26b-5p (originally named miR-26b). MiR-26b in OLP has been reported to inhibit oral keratinocyte apoptosis by directly targeting PKCδ (40). Thus, circRNAs may adsorb downstream miRNAs and act as molecular sponges to regulate miRNAs, thereby changing mRNA expression level. Further research needs to be conducted to study the interactions between circRNAs and downstream target miRNAs and mRNAs in OLP.

Conclusions

In this study, an expression profile of abnormally expressed circRNAs in OLP was mapped for the first time. A total of 135 circRNAs were found to be differentially expressed between OLP and normal oral mucosa tissues. Of this 135 circRNAs, 19 were novel. The GO function and KEGG functional pathways analyses showed that the identified circRNAs might play important OLP roles. A circRNAs–microRNAs network was constructed to understand better the roles of circRNAs in the occurrence and development of OLP. Our study results may help other researchers elucidate the mechanism of OLP development and provide new clinical diagnostic markers and therapeutic targets.

Acknowledgments

We would like to thank Professor D.J. Cao and Professor Y.P. Pu for providing the normal oral mucosa tissues and CloudSeq Biotech (Shanghai, China) for providing the high-throughput sequencing service.
Funding: National Key R&D Program of China (81170968).

Footnote

Reporting Checklist: The authors have completed the MDAR reporting checklist. Available at http://dx.doi.org/10.21037/apm-20-2253

Data Sharing Statement: Available at http://dx.doi.org/10.21037/apm-20-2253

Peer Review File: Available at http://dx.doi.org/10.21037/apm-20-2253

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-2253). 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Ninth People's Hospital of Shanghai Jiaotong University School of Medicine [No. 89 (2012) 21]

and informed consent was taken from all the patients.

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Cite this article as: Song Y, Xu S, Shao Y, Ge S, Zhou H. Expression profile of circular RNAs in oral lichen planus. Ann Palliat Med 2021;10(5):5205-5217. doi: 10.21037/apm-20-2253

