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ORIGINAL RESEARCH

Comprehensive Analysis of lncRNA/circRNAs-miRNA-mRNA Networks of Oral Lichen Planus

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Background: Oral lichen planus (OLP) is T cell-mediated inflammatory disease affecting the oral mucosa, and its molecular mechanism remains poorly understood.

Objective: This study aimed to screen for OLP-related hub genes and construct a network of competing endogenous RNAs (ceRNAs) to explore the crucial mechanisms involved in the disease.

Methods: Proteomic and transcriptomic sequencing were performed on oral mucosa collected from OLP patients and healthy participants, respectively. Limma package was used to screen differentially expressed proteins (DEPs) and RNAs between groups. Shared genes between DEPs and DE mRNAs (DEGs) were subjected to functional enrichment analysis and protein-protein interaction (PPI) network construction. Weighted gene co-expression network analysis was used to screen for OLP-related genes. Furthermore, the OLP-related genes in the most significant PPI modules were defined as key genes, and LASSO analysis was further used to screen hub genes from the key genes. The area under curve (AUC) value was calculated from receiver operating characteristic curves to assess the diagnostic efficacy of hub genes. Finally, a ceRNAs regulatory network was constructed, and the hub genes were validated using qPCR analysis.

Results: In the disease group, 103 shared DEGs (85 upregulated and 18 downregulated) were identified from both transcriptomic and proteomic data. These DEGs were involved in pathways such as antigen processing and presentation. COTL1, OAS2, HLA-A, and HLA-DPA1 were identified as hub genes. They had good diagnostic efficacy for OLP, with all AUC value exceeding 0.7 based on the transcriptomic and proteomic data. LncRNA MIR155HG regulated COTL1 and OAS2 by competitively binding to hsa-miR-1233-5p. Moreover, PCR analysis validated that these four hub genes were all highly expressed in OLP tissue compared with control tissue ($P < 0.05$).

Conclusion: mRNAs, proteins and non-coding RNAs provide clues to study the mechanisms of OLP. Furthermore, circRNAs/lncRNAs-miRNAs-mRNA networks provide more information about potential novel mechanisms and diagnostic treatments for OLP.

Keywords: oral lichen planus, competing endogenous RNAs, weighted gene co-expression network analysis, non-coding RNAs

Introduction

Oral lichen planus (OLP), which is T cell-mediated inflammatory response of epithelial cells to uncertain antigens, is a chronic inflammatory autoimmune disease in the oral mucosa.[1] The global prevalence of OLP is 1.01%, with prevalence increasing and progression accelerating in people over 40 years of age, but without significant gender preference.[2] A systematic review showed that the percentage of malignant transformation of OLP was 2.28% based on the 10 highest-quality studies, suggesting epithelial dysplasia and the possibility of squamous cell carcinoma.[3] There is no consensus on the clinical subtypes of OLP, but several variants usually exist, including atrophic, erosive, bullous plaque-like, and reticular types. The reticular type presents as a classic white lace-striped lesion with hyperkeratotic

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plaques, and the atrophic and erosive types show erythema and ulcerative lesions, respectively.[4,5] The pathogenesis of OLP remains unclear, but there is evidence that innate immune cells and oral keratinocytes mount an immune response to OLP-mediated antigens, ultimately leading to increased expression of cytokines, chemokines and adhesion molecules. The aforementioned factors enrich T cells and mast cells to diseased lesions, culminating in the death of keratinocytes and destruction of the mucosal basement membrane.[6]

The primary treatment for OLP typically involves topical corticosteroids,[7,8] miconazole,[9] and calcineurin inhibitors such as topical tacrolimus.[10] These treatments can control the T cell-mediated inflammatory processes, but none offer a definitive cure for OLP, as the condition marked by alternating periods of flare-ups and remission.[11] In addition to these therapies, recent studies have expanded the treatment options to include glucocorticoids like fluocinonide, which have shown promise in both systemic disease models and as part of topical treatment protocols for OLP.[12] Nevertheless, there remains a significant need for further research into the mechanisms underlying OLP and the identification of novel therapeutic strategies to improve clinical outcomes.

Proteomics is the study of a large number of proteins in biological systems.[13] As intermediate phenotypes of disease, proteins can explain the relationship between genetic factors and clinical outcomes.[14] Proteomic studies of tumor-associated proteins, autoantigens and pathogenic antigens provide new ideas and approaches for cancer, autoimmunity and infection.[15] In recent years, proteomics has been widely used to identify biomarkers to detect cancer, monitor tumor response to therapy, understand the mechanisms of cancer development, and design new therapeutic regimens.[16] The transcriptome is the study of how genes are regulated and expressed in different biological environments.[17] Transcriptome analysis plays a major role in the study of differentially expressed genes, disease biomarkers, disease heterogeneity and evolution, disease drug resistance, swelling microenvironment, and immunotherapy.[17] The integration of multi-omics approaches has allowed us to better understand disease mechanisms. However, no transcriptomic combined with proteomic studies have been reported in OLP.

Transcripts include both coding and non-coding RNAs (ncRNAs). The ncRNAs, including circular RNAs (circRNAs), long noncoding RNAs (lncRNAs), and microRNAs (miRNAs), play crucial roles in a variety of biological processes.[18] Competing endogenous RNAs (ceRNAs) are a large-scale regulatory network across the transcriptome formed by crosstalk between coding RNAs (mRNAs) and ncRNAs (such as lncRNAs and circRNAs) through miRNA response elements.[19] Many OLP-associated ceRNA networks have been identified, and increasing studies suggests that perturbation of key interactions in these networks may contribute to OLP.[20–22] CircHLA-C was found to be a circRNA differentially expressed in the OLP that could act on the cellular regulatory network by binding to miRNAs such as hsa-miR-26a-5p, hsa-miR-129-5p, hsa-miR-29a-3p and hsa-miR-4739 through complementary pairing.[21] The NEAT1/XIST-miR-15a-5p/miR-155-5p-APP/IL1B signaling axis may play an important role in the malignant transformation of OLP in the constructed lncRNAs-miRNAs-mRNAs ceRNA network.[22] However, the ceRNA regulation mechanisms in OLP have not been fully elucidated because of the unknown pathogenesis. Exploring the molecular mechanisms of OLP is crucial and may help to identify accurate biomarkers for the diagnosis and treatment of OLP.

Given the complexity of OLP and the limited understanding of its molecular mechanisms, the aim of this study was to integrate proteomics and transcriptomics to explain the molecular mechanisms of OLP from a ceRNA perspective. By combining these approaches, we aimed to identify key molecules and interactions that regulate the inflammatory processes involved in OLP, ultimately uncovering potential biomarkers or therapeutic targets for this condition.

Materials and Methods

Study Design

This study was designed as a prospective cross-sectional study. Participation was on a voluntary basis and all participants signed an informed consent form. This study complied with the guidelines of the Declaration of Helsinki. The study was approved by the Ethics Committee of Huashan Hospital, Fudan University (Approval No. KY2019-589).

Patients attending the Department of Oral Mucosa at Huashan Hospital of Fudan University from December 2019 to June 2022 were included in the OLP group according to the OLP diagnostic criteria.[1] The specific clinical and histopathologic diagnostic criteria were as follows: most of the OLP lesions were symmetrical, and could occur in any

part of the oral mucosa, mostly in the buccal mucosa, tongue dorsum, and gum. The lesion site was mainly white reticulation or plaque, and the mucosa around the lesion manifested as congestion, erosion, and ulceration. The was no specific pathological manifestations and the main histopathological criteria for OLP included: banded inflammatory cell infiltration dominated by well-defined lymphocytes and limited to the superficial layer of connective tissue, basal cell liquefaction degeneration, no epithelial dysplasia.[1,11,23] Inclusion criteria for the OLP group: 1) patients aged 18 years or older; 2) patients diagnosed with OLP based on medical history, clinical manifestations, and pathological examination; and 3) patients willing to sign an informed consent form and provide a personal medical history. Exclusion criteria for the OLP group: 1) patients with other established oral mucosal diseases; 2) patients with serious systemic diseases such as heart disease or cancers; 3) patients with various extrinsic factors that could trigger a lichenoid-like reaction; 4) pregnant and lactating woman, as well as patient preparing for pregnancy during the trial period; and 5) patient suffering from any mental illness or other conditions that could lead to a legal determination of limited capacity to act.

The control group consisted of volunteers who underwent extraction of impacted teeth on the buccal side at our hospital's outpatient department during the same period. Normal oral mucosa without inflammation or oral mucosal lesions was used as the control. The panoramic X-ray images of the volunteers before their tooth extractions were shown in Supplementary Figure 1.

Reticular/Erosive/Ulcerative Lesion (REU) Score of the Patients with OLP

Patients with OLP were evaluated clinically and histopathologically according to the previously described diagnostic criteria.[11,23] The REU score was performed based on the clinical manifestation of patients with OLP. Specifically, the scoring criteria were as follows: reticulation/hyperkeratosis (R): yes (1), no (0); congestive erosive type (E); ulcerative type (U): no lesion (0), lesion area < 100 mm^2 (1), 100 mm^2 ≤ lesion area < 300 mm^2 (2), lesion area > 300 mm^2 (3); total score = R + E × 1.5 + U × 2.

Tissue Sample Collection

Patients and healthy subjects routinely rinsed their mouths with compound chlorhexidine mouthwash 3 times before the surgery. In the OLP group, lesional tissues were collected (tissue size: 1.0 cm × 0.6 cm), whereas in the control group, oral mucosal samples were obtained from individuals who had impacted wisdom teeth extracted without inflammatory status. Samples from each group were divided into two equal parts, one was fixed in formaldehyde for routine histological diagnosis, and the other was collected, immediately lysed and extracted on the same day, preserved in liquid nitrogen until used for subsequent transcriptomic and proteomic analysis.

Liquid Chromatography-Mass Spectrometry (LC-MS) Analysis

The obtained tissue was dissolved and mixed in lysis buffer. Subsequently, the solution was reduced with 10 mM DTT at 37 degrees Celsius for 30 minutes, followed by alkylation with 30 mM iodoacetamide at 25 degrees Celsius for 45 minutes. Then, buffer exchange was performed using digestion buffer, and the samples were digested with trypsin for 12 hours. Protein concentration was estimated using the BCA method.

LC-MS analysis was carried out using the nanoflow EASYnLC 1200 system (Thermo Fisher Scientific, Odense, Denmark) coupled with the Orbitrap Exploris480 mass spectrometer (Thermo Fisher Scientific, Bremen, Germany). All analyses were carried out using a single-column system. The samples were analyzed on a homemade C18 analytical column (75 μm inner diameter × 25 cm, ReproSil-Pur 120 C18-AQ, 1.9 μm particle size, Dr. Maisch GmbH, Germany). The elution gradient is shown in Supplementary Tables 1 and 2. The results were processed using the UniProt human protein database (75,004 entries) and analyzed with Protein Discoverer (version 2.4, Thermo Fisher Scientific) and Mascot (version 2.7.0, Matrix Science).

RNA Extraction and Library Construction

The TRIzol (Invitrogen, Shanghai, China) was used to extract the total RNA from the samples. The integrity and purity of the RNA were assessed by 2% agarose gel electrophoresis and spectrophotometry. The NEBNext® Ultra™ RNA Library Prep kit for Illumina® (New England Biolabs, Ipswich, MA, USA) was employed for cDNA library preparation.

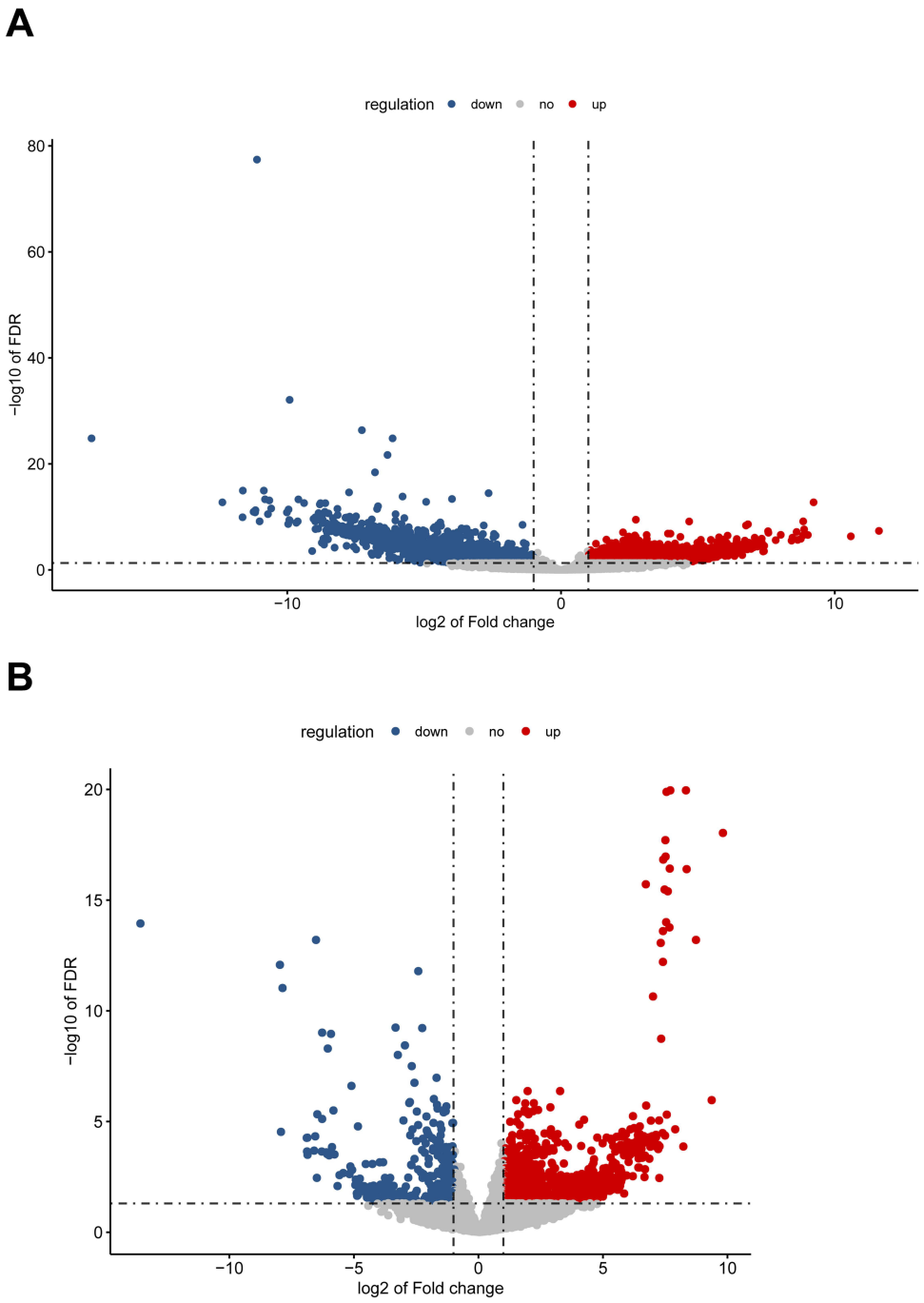

Figure 1 Volcano maps of genes and proteins in the oral mucosa in oral lichen planus compared to healthy participants. (**A**) Genes expression volcano maps; (**B**) Proteins expression volcano maps.

Sequence Alignment

After filtering out low-quality sequences (reads with adapter sequences, low-quality bases >50%, and/or unknown nucleotides >10%), sequences with high quality were aligned to the human genome (version hg19) using the tophat2 software.

Screening of Differentially Expressed RNAs

The limma (version 3.48.3)[24] package of the R software was used to screen for differentially expressed proteins (DEPs), differentially expressed mRNAs (DEGs), differentially expressed circRNA (DEcirs), and differentially expressed

lncRNAs (DElncs) between OLP and normal. False discovery rate < 0.05 and |log fold change (FC)| > 1 were set as screening thresholds for DEPs, DEGs, and DElncs. circRNAs with $P < 0.05$ and |logFC| >1 were identified as DEcirs. In addition, we also used the R VennDetail package (version 1.2.0) to take the intersection of DEPs and DEMs as common genes for subsequent analysis.

Enrichment and Protein-Protein Interaction (PPI) Network Analyses for Common mRNAs

The R clusterProfiler package[25] was used to generate the Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis on common mRNAs. Terms with $P < 0.05$ were defined with statistical significances. The STRING (version 11.5) database[26] was used for the construction of PPI networks for the proteins corresponding to common genes. The interaction score was set to 0.4. Besides, we further analyzed the different modules aggregated in the PPI network using the cytoscape plugin MCODE (version 4.2),[27] where the score was set to greater than 5.

Identification of Hub Genes

Firstly, common genes were subjected to weighted gene co-expression network analysis (WGCNA, version 1.71)[28] to screen for disease-associated modular genes, using the presence or absence of disease as a phenotypic trait. Secondly, the venn analysis of disease-associated module genes and PPI module genes was used to obtain the intersecting genes as key genes using the R VennDetail package (version 1.2.0, https://github.com/guokai8/VennDetail), and functional enrichment analysis was performed using the R clusterProfiler Package (version 4.4.4, http://bioconductor.org/packages/release/bioc/html/clusterProfiler.html), with P value < 0.05 as threshold. Then, the R package glmnet (version 4.0–2)[29] for LASSO cox regression was used for further screening of the above key genes. Ten-fold cross-validation was performed to obtain the best λ value. Finally genes with non-zero regression coefficients were defined as hub genes and formed the most optimal hub genes.

Evaluation of the Diagnostic Efficacy of Hub Genes

Based on proteomic and transcriptomic data, the R package pROC (version 18.0)[30] was used to create receiver operating characteristic (ROC) curves for hub genes to assess the diagnostic value. A higher area under curve (AUC) value represents a stronger diagnostic value. The relative expression of hub genes and their corresponding proteins were compared between groups using *t*-test.

Prediction of Co-Expression Regulatory Pairs

We calculated the co-expression relationships of lncRNA-mRNA as well as circRNA-mRNA in hub genes based on the Spearman coefficient method. The threshold for the relationship pairs was set at r > 0.7 and $P < 0.05$. Miranda was used for prediction of targeting miRNAs for DElncs, DEcirs co-expressed with hub genes to obtain miRNA-lncRNA and miRNA-circRNA relationship pairs, respectively. The threshold was set to en = −20 and score = 165. miRWalk (version 3.0)[31] was used to predict miRNA-mRNA regulatory pairs, and the threshold was set to score>0.95. Finally, based on the above relation pairs, we constructed the ceRNA network.

Expression Validation of the Hub Genes

Six control oral tissues without OLP and six OLP samples were obtained and used for qPCR analysis. Total RNA of each sample was isolated using TRIZOL kit (TaKaRa, 9109). GAPDH was used as the internal control.

Statistical Analysis

Data were visualized and analyzed in Prism (GraphPad, San Diego, CA, USA). Data were presented as mean ± standard deviation (SD). Student's *t*-test was used to analyze the significance of the data, and $P < 0.05$ was considered statistically significant.

Results

Demographics and Clinical Characteristics of the Patients with OLP

In our study, control samples were obtained from 16 volunteers (6 males, 10 females, mean age 42 ± 14 years old) who underwent the extraction of impacted wisdom teeth, while OLP samples were collected from19 patients with OLP (7 males, 12 females, mean age 53 ± 15 years old). Because some patients requested privacy protection, we provided clinical data for 10 patients with OLP, including demographic, REU score and associated condition (Supplementary Table 3). Oral mucosa photographs and HE staining images from 6 patients with OLP were shown in Supplementary Figure 2.

Screening of Differentially Expressed RNAs and Proteins

We screened for differentially expressed RNAs between OLP and control samples. Finally, 1634 DEGs (66 up-regulated, 972 down-regulated), 117 DElncs (36 up-regulated, 81 down- regulated), 43 DEircs (15 up-regulated, 28 down-regulated), and 1773 DEPs (1492 up-regulated, 274 down-regulated) were screened out. mRNAs and proteins expression patterns between OLP and control groups are exhibited in Figure 1A and 1B.

Functional Analysis of Shared Genes

We obtained a total of 85 shared genes upregulated in the disease group and 18 genes downregulated in the disease group that were common to both transcriptomic and proteomic data. Subsequently, in order to investigate the possible functions of these genes, this study performed GO and KEGG enrichment analyses. These 103 genes were enriched in 187 GO terms and 12 KEGG pathways. All KEGG pathways and the top 5 GO molecular function (GO−MF), GO biological process (GO−BP), and GO cell component (GO−CC) terms according to p value were shown in Figure 2. The shared genes involved in immune response-related functions like antigen processing and presentation of endogenous peptide antigen, phagocytic vesicle membrane, peptide antigen binding (Figure 2A). KEGG pathways mainly included in antigen processing and autoimmune response-related pathways: viral myocarditis, antigen processing and presentation, and allograft rejection (Figure 2B).

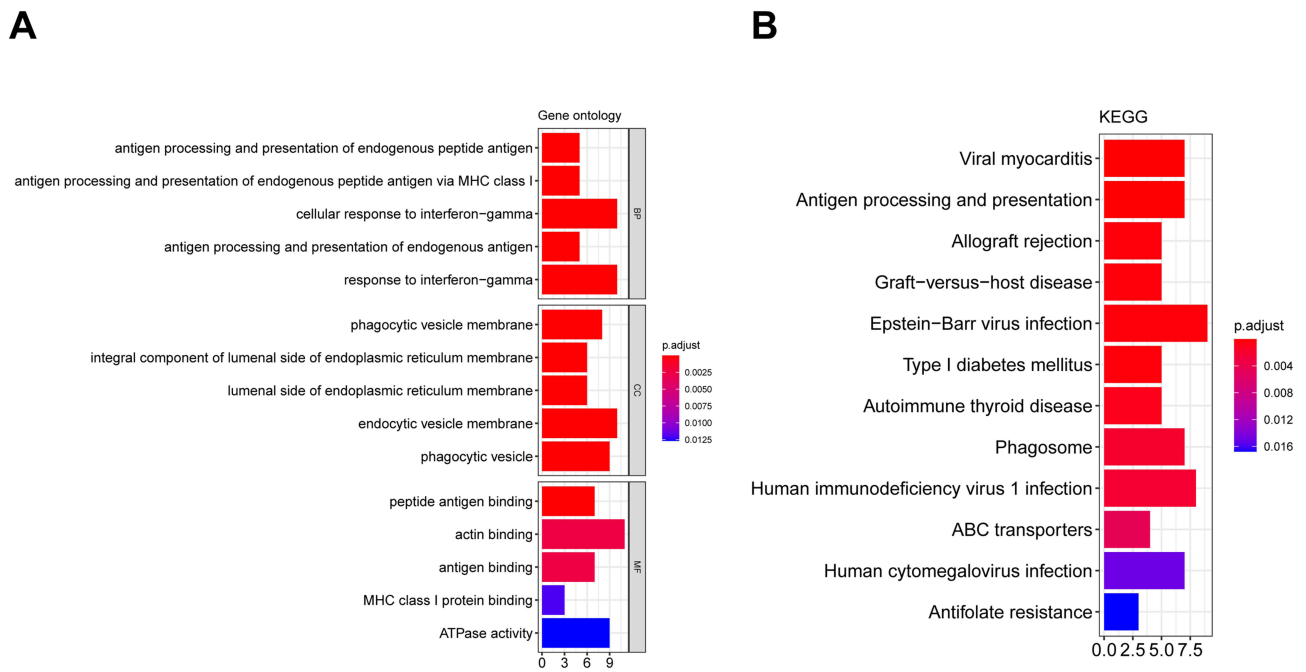

Figure 2 Functional enrichment analyses of shared genes. (**A**) Gene Ontology analysis of shared genes; (**B**) Kyoto Encyclopedia of Genes and Genomes analysis of shared genes. MF, BP, CC represent molecular function, biological process, and cell component, respectively.

Regulatory Relationships Between Proteins

To explore the possible interactions between shared genes, we constructed a PPI network. This network contained a total of 100 proteins and 427 relationship pairs (Figure 3A). Further modular analysis revealed (Figure 3B) that 16 proteins constituted a reciprocal network containing 58 relationship pairs. These 16 proteins involved 206 GO−BP, 39 GO−CC, and 31 GO−MF terms, and only the terms with the top 5 P values were shown. As shown in Figure 3C, these proteins mainly involved in antigen processing and presentation of exogenous peptide antigen, integral component of lumenal side of endoplasmic reticulum membrane, and peptide antigen binding. The mainly involved KEGG pathways included antigen processing and presentation, epstein−barr virus infection, and allograft rejection (Figure 3D). Only the top 10 pathways sorted by *P* value were displayed.

Screening for OLP-Related Genes

In order to find the OLP-related genes, we performed WGCNA on the shared genes. As shown in Figure 4A, when the soft-threshold power was set to 14, the scale-free topology index was 0.85, indicating that the network approximates the scale-free distribution. The dendrograms analysis of the gene showed a total of 12 modules (Figure 4B). Subsequently, we performed association analysis between modules and phenotypes and found that three modules, Meblack, Memagenta and Mepink, had high positive correlations with disease ($r > 0.8$, $P < 0.01$) (Figure 4C). The 207 genes contained in the above three modules were define d as OLP-associated genes and were used in the subsequent analysis.

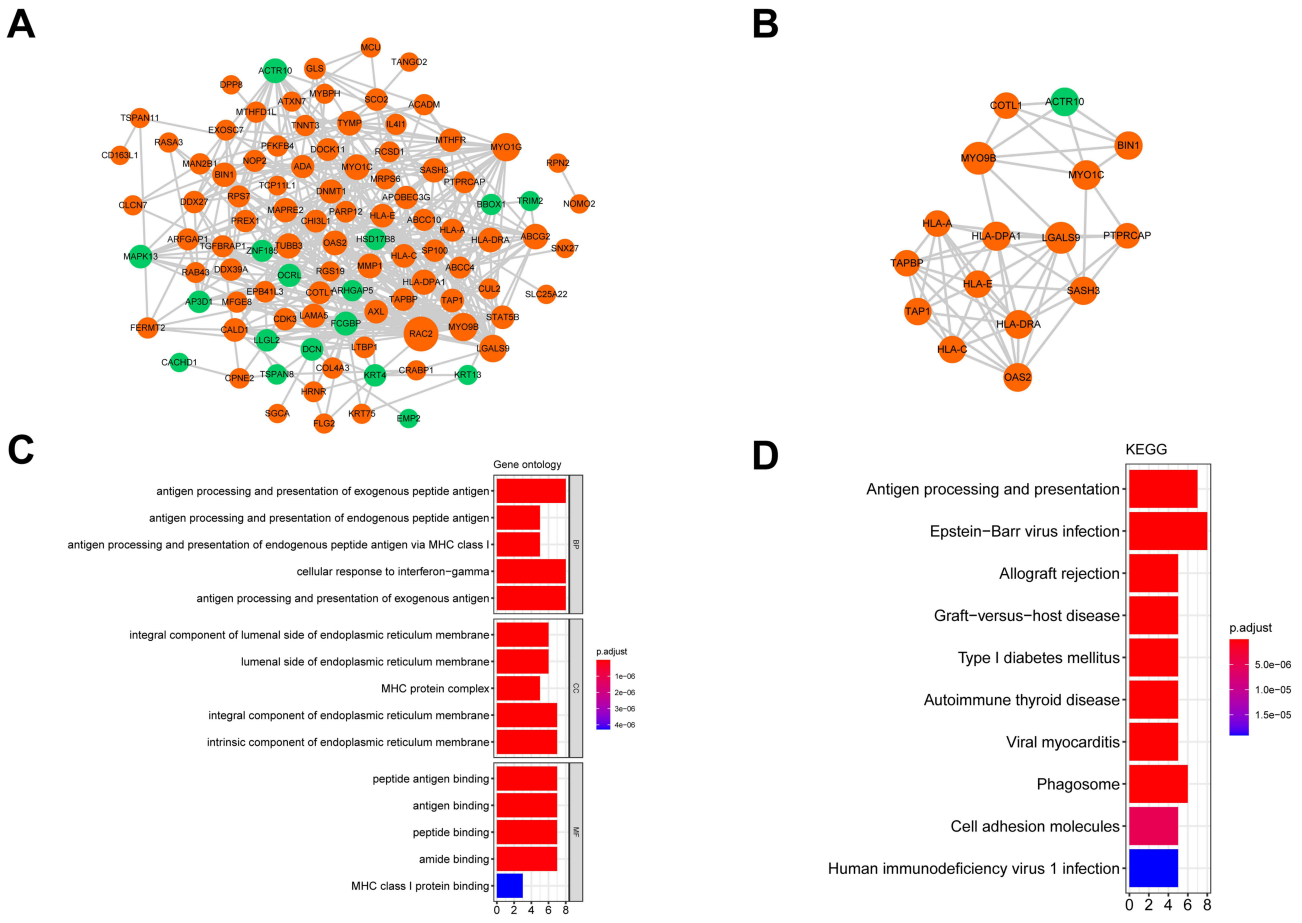

Figure 3 Protein interaction analysis. (**A**) protein-protein interaction network; (**B**) The PPI module with the most significant clustering; (**C**) Gene Ontology analysis of module genes; (**D**) Kyoto Encyclopedia of Genes and Genomes of modules genes. MF, BP, CC represent molecular function, biological process, and cell component, respectively.

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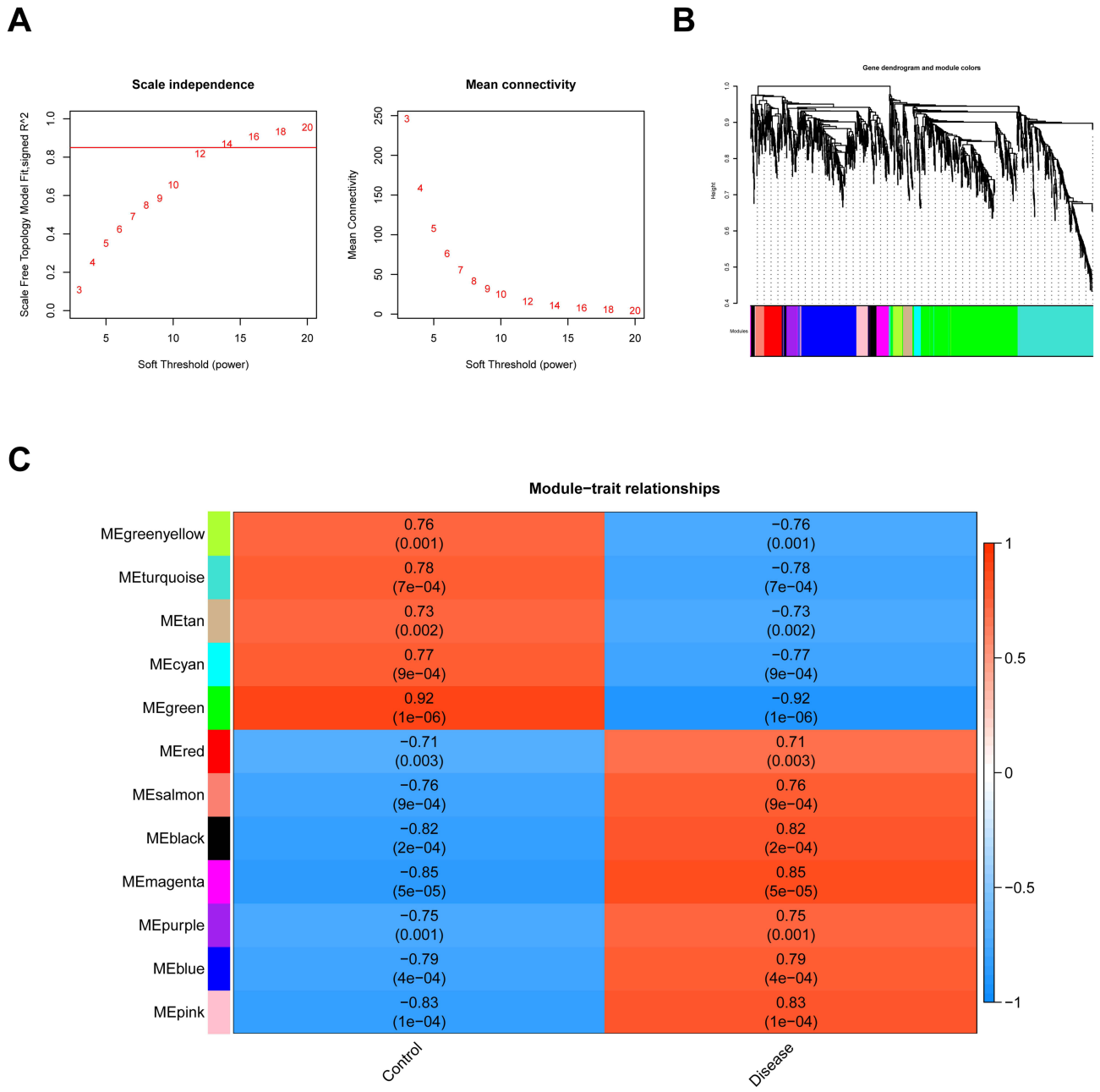

Figure 4 Screening of oral lichen planus-related genes. (**A**) Scale Independence and mean connectivity analysis for various soft threshold powers; (**B**) Clustering dendrograms of mRNAs; (**C**) Heat map of module and phenotype association analysis. Different colors below indicate different co-expression modules.

The Hub Gene in OLP

Six of the OLP-related genes were shared with PPI module genes (HLA-DRA, COTL1, SASH3, OAS2, HLA-A, HLA-DPA1). We performed functional analysis of these six key genes. The results revealed that these 6 key genes were involved in 118 GO BP, 32 GO CC, and 12 GO MF. These GO terms mainly included interferon-gamma-mediated signaling pathway, MHC protein complex, and peptide antigen binding (Figure 5A). In addition, these 6 key genes were involved in 23 KEGG pathways, mainly included autoimmune thyroid disease, antigen processing and presentation, and cell adhesion molecules (Figure 5B). Among which, cell adhesion molecules are related to pathogenesis of OLP.[32]

LASSO was applied to further screen hub genes from the key genes, resulting in four hub genes: HLA−DPA1, OAS2, COTL1, and HLA−A (Figure 5C and 5D).

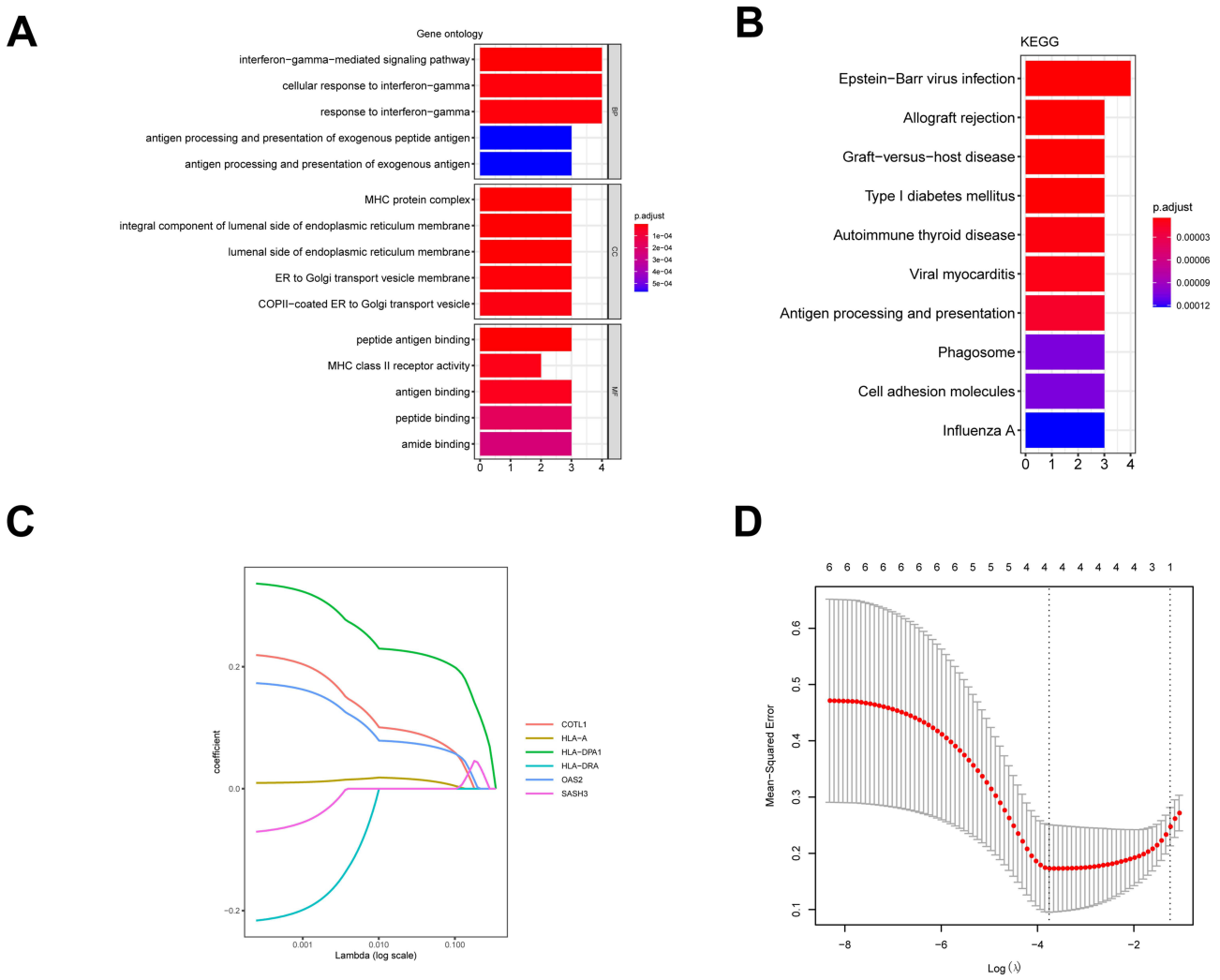

Figure 5 Analysis of key genes. (**A**) Gene Ontology analysis of key genes; (**B**) Kyoto Encyclopedia of Genes and Genomes of key genes. (**C** and **D**) LASSO analysis for selecting hub genes. MF, BP, CC represent molecular function, biological process, and cell component, respectively.

Diagnostic Efficacy of Hub Gene

Based on the transcriptomic dataset, we performed ROC curve analysis for the four hub genes. The results showed that HLA-A, COTL1, OAS2, and HLA-DPA1 had AUC values of 0.760, 0.920, 0.840, and 0.800, respectively (Figure 6A). Considering the proteomic data, we found that the AUCs of all three hub genes were 1.000 except for HLA-DPA1 (0.929) (Figure 6B). In addition, we visualized the expression of hub genes and proteins. All four genes were significantly over-expressed in the OLP samples (Figure 6C and 6D). qPCR analysis also validated that these genes were all up-regulated in OLP when compared with control sample (Figure 6E, $P < 0.05$).

Construction of a ceRNA Network

According to the method described, we obtained a total of 14 lncRNA-mRNA pairs, 1 circRNA-mRNA pair, 67 miRNA-lncRNA pairs, 8 miRNA-circRNA pairs, and 50 miRNA-lncRNA relationship pairs. Based on the above relationship pairs, we constructed a ceRNA network containing 83 nodes and 136 relationship pairs (Figure 7). This network included 4 hub genes, 1 circRNA, 11 lncRNAs, and 67 miRNAs. Key ceRNAs, such as MIR155HG-hsa-miR-1233-5p-COTL1 /OAS2 were identified in the network.

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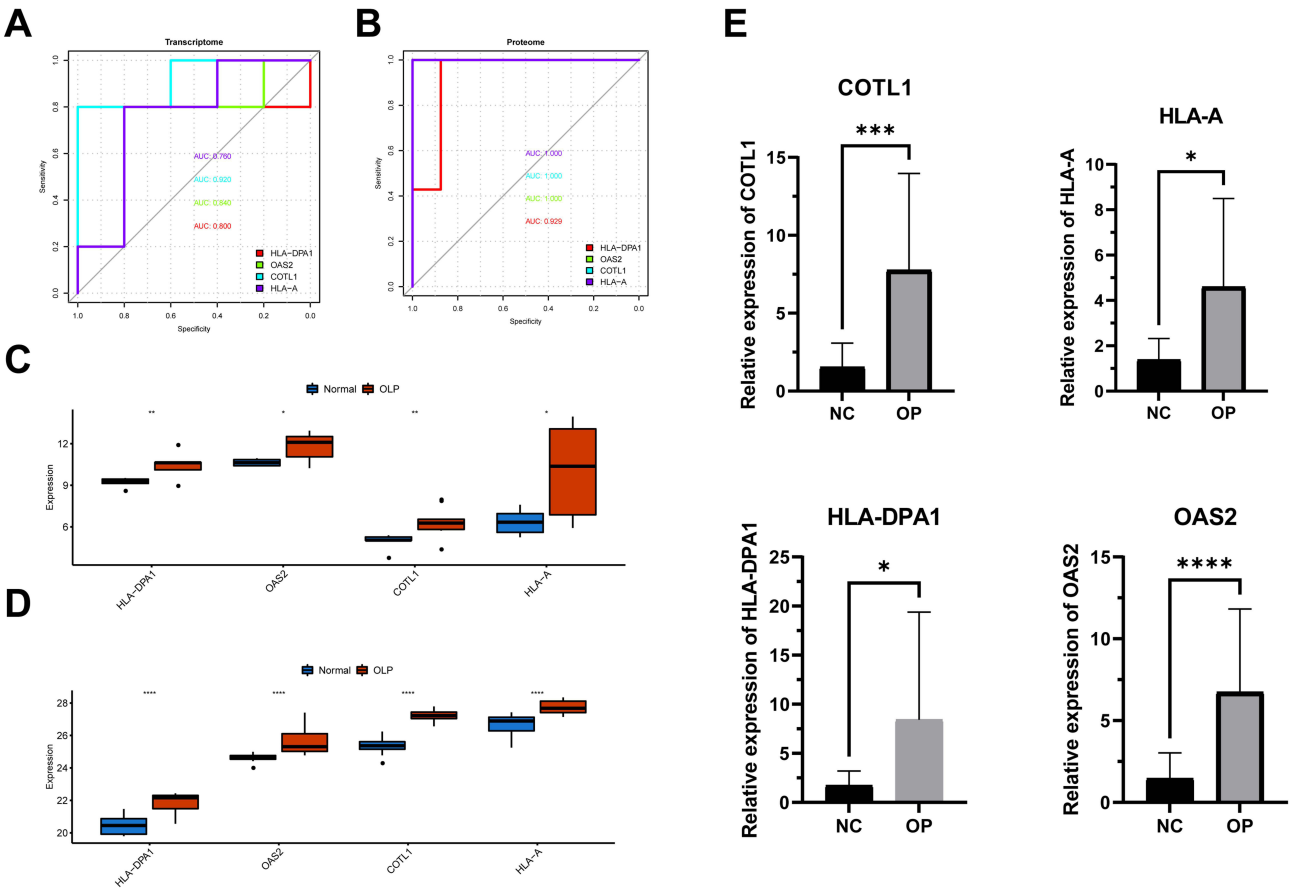

Figure 6 Analysis of key genes. (**A**) operating characteristic (ROC) curves of key genes in transcriptomic dataset; (**B**) ROC curves of key genes in protemoic dataset; (**C**) Relative mRNA expression of hub genes; (**D**) Relative protein expression of hub genes; (**E**) Validation of the hub genes. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$; ****, $P < 0.0001$.

Discussion

This study used transcriptome and proteome sequencing data from which we screened molecules that were differentially expressed in both data sets. Further analyses, including PPI network, WGCNA, and LASSO, identified four hub genes (HLA-DPA1, OAS2, COTL1, and HLA-A) in OLP. These genes had good predictive performance for OLP, with all AUC value exceeding 0.7 based on the transcriptomic and proteomic data. Finally, this study constructed a ceRNA network containing 136 relationship pairs. From this network, MIR155HG could regulate COTL1 and OAS2 by competitively binding to hsa-miR-1233-5p.

Major histocompatibility complexes (MHC) is known as human leukocyte antigens (HLA) in humans.[33] The HLA genes are often considered to be central to pathogenic autoimmune responses, providing a mass of antigenic peptides for T cells and allow the immune system to distinguish between self and non-self.[34] Prior studies that have noted the close association of HLA in susceptibility to many autoimmune diseases.[33] In our current observations showed that mRNA levels of both HLA-A and HLA-DPA1 were significantly upregulated in OLP patients. The researchers found that in a population of 73 Macedonian patients with OLP, HLA-A9 and HLA-A8 were recognized as carriers with a propensity for the erosive OLP, and the reticular OLP is HLA-A3 antigen.[35] Moreover, HLA-A were demonstrated to be related to some immune disease like psoriasis.[36,37] While how HLA-A affect these immune disease remains controversy which exhibiting as some are susceptible, some are protective.[36] As for the hub gene HLA-DPA1, one previous study reported that HLA-DPA1 was overexpressed in OLP and is associated with Th1 autoimmunity.[38] Obviously, specific alleles of the HLA gene have been found to be strongly associated with the development and progression of OLP, but available

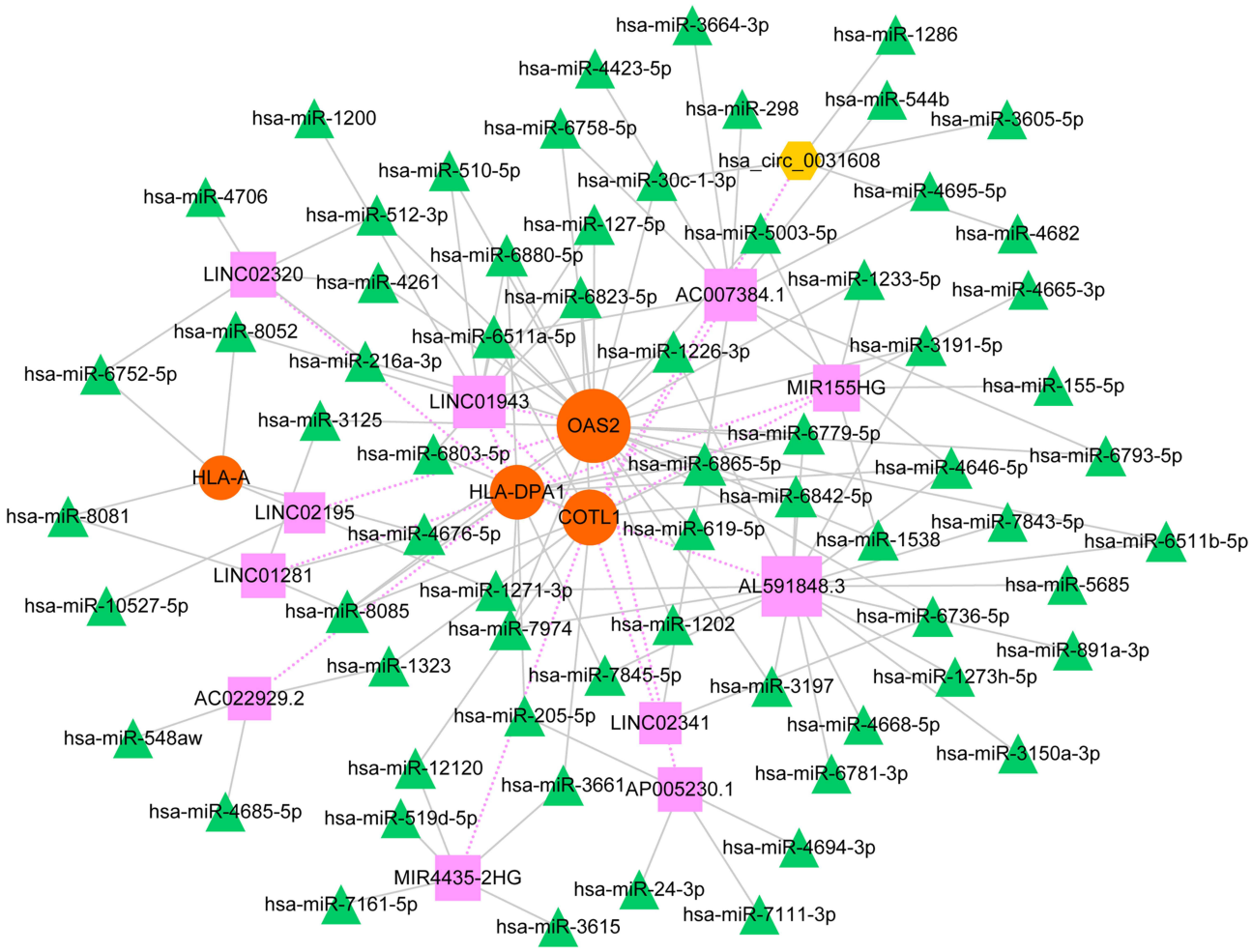

Figure 7 A network of competing endogenous RNAs. Red circles represent hub genes, pink squares represent up-regulated lncRNAs, yellow hexagons represent up-regulated circRNAs, green represent miRNAs, pink dotted lines represent co-expression pairs (lncRNA-mRNA and circRNA-mRNA), and node sizes represent the size of degree values.

evidences are rather difficult to interpret the genetic associations and pathogenic mechanisms between HLA and susceptibility to OLP. This is an important issue for future research.

Coactosin-like protein 1 (COTL1), a member of the actin-depolymerizing factor (ADF)/cofilin family, typically binds to actin filaments to regulate the actin cytoskeleton.[39] Studies on COTL1 in OLP have not been found. In some immune disease, roles of COTL1 have been reported. Upregulation of COTL1 may affect 5-lipoxygenase activity involved in leukotriene biosynthesis and mediates the inflammatory response in rheumatoid arthritis. Notably, COTL1 was also found to be involved in cancer progression. Some studies had reported that COTL1 expression was up-regulated in small cell lung cancer tissue with positive immunohistochemical result, and also inhibited breast cancer progression through activation of IL-24/PERP and inhibition of non-classical TGFβ signaling.[40,41] The latest research had found that COTL1 was highly expressed in most cancers and positively correlated with immune checkpoints and immune-infiltrating cells, suggesting potential of COTL1 as an immunologic and prognostic biomarker.[42] According to these known findings, we could infer that COTL1 might influence OLP progression in aspects of immunity and inflammation, and the antitumor relevance of COTL1 might be useful in exploring precancerous lesions of OLP.

2′-5′ oligoadenylate synthetase 2 (OAS2), is a member of the OAS family, may destabilize virus-derived dsRNA with RNase L function, also involved in immune response or antiviral activity.[40,43,44] OAS2 expression was upregulated in Systemic lupus erythematosus (SLE) patients compared to healthy participants. Knockdown of OAS2 inhibits the effect of IFN-α-2a on IFN-α and IL-1β, where IFNs mediate multiple inflammatory responses.[45] In psoriasis, levels of OAS2

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are upregulated in both epidermis and serum and are related to disease-related score,[44] indicating that OAS2 can be a novel biomarker for disease activity. No correlation between OAS2 and OLP has been reported. In our study, like the above immune disease (RA, SLE, or psoriasis), OAS2 levels were also highly expressed in OLP samples, indicating their potential indicating and predicting role in OLP.

Enrichment analysis revealed hub genes involved in T cell mediated immunity. OLP is a type of inflammatory disease regulated by T cells that affects the oral mucosa. In the pathogenesis of OLP, CD4+ T helper (Th) cells activate CD8+ cytotoxic T cells (CTLs) through the release of cytokines including interleukin (IL)-2 and interferon (IFN)-γ. Further, activated lesional CTLs secrete cytokines such as TNF to induce HLA-DR expression in basal keratinocytes and activation of shikimate cells. Finally, activated CTLs trigger apoptosis of basal keratinocytes, leading to clinical and histological manifestations of OLP.[46] In addition, accumulating evidence has highlighted the role of oxidative stress in various diseases, including inflammatory conditions and autoimmune diseases.[47] In the pathogenesis of OLP, oxidative stress is also play a critical role.[48] The infiltration of T lymphocytes in the subepithelial layer of OLP lesions promotes the local production of cytokines, which can further stimulate the generation of ROS.[49] ROS is an essential mediator of apoptosis, a hallmark of OLP, and can contribute to the dysfunction of keratinocytes and impair their apoptosis process.[50]

The MIR155 host gene (MIR155HG) is an important molecule in ceRNA network in the present study. It can encode the micropeptide miPEP155 (P155) and is over expressed in inflammatory antigen-presenting cells, resulting in the interaction of P155 with the binding domain of heat shock homologue protein 70 (HSC70), which is a chaperone essential in antigen transport and presentation in dendritic cells (DCs). P155 regulates the major histocompatibility complex class II-mediated antigen presentation by disrupting the HSC70-HSP90 mechanism.[51] P155 alleviated the inflammatory phenotype of psoriatic mice, specifically inhibiting epidermal proliferation and dermal infiltration and reducing the number of epidermal Ki67+ cells.[51] In this study, we found that MIR155HG could bind competitively with hsa-miR-1233-5p to regulate the expression of OAS2. Interestingly, we found that MIR155HG also competitively binds to hsa-miR-1233-5p to regulate COTL1. More experiments are needed to verify the specific regulatory mechanism.

In this study, we identified four hub genes in OLP by a comprehensive bioinformatics analysis combining transcriptomic and proteomic data. Furthermore, the MIR155HG-hsa-miR-1233-5p-COTL1/OAS2 axis was found to have a critical role in the progression of OLP. The present findings may provide new insights into the pathogenesis of OLP and suggest potential therapeutic targets for OLP. Despite these promising results, limitations remain. First, the sample size was small, which may lead to heterogeneity in clinical samples. It is necessary to verify the robustness of the results in a larger sample size cohort. Second, only the mRNA differential expression levels of hub genes were validated in clinical samples, the expression of key lncRNA such as MIR155HG as well as the key ceRNAs like MIR155HG-hsa-miR-1233-5p-COTL1/OAS2 needs to be validated with external data and in vitro and vivo experiments. Finally, the diagnostic efficacy of hub genes was not validated in more clinical cohorts. Overall, more experiments are required for further verifying the findings in this study.

In conclusion, our findings revealed that hub genes like HLA-DPA1, OAS2, COTL1, and HLA-A may play a crucial role in promoting OLP development. ceRNA network analysis also provided some clues to investigate the mechanisms of OLP. Moreover, these genes could contribute to OLP pathogenesis through some immune-related functions or pathway like antigen processing and presentation, and cell adhesion molecules. Furthermore, key ceRNA networks such as MIR155HG-hsa-miR-1233-5p-COTL1/OAS2 axis may participate in OLP development, providing valuable insights into the mechanisms underlying the disease.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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