Bioinformatics analysis of differentially expressed genes and their potentially interacting miRNAs in oral lichen planus

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Abstract

Background Oral lichen planus (OLP) was a common oral mucosal disease. However, the etiology and pathogenesis of OLP were still limited. This research was designed to identify the differentially expressed genes and relative miRNAs in OLP.

Methods and Results The OLP microarray dataset (GSE52130) was download from the Gene Expression Omnibus (GEO) database. R software was used to identify differentially expressed genes between the OLP samples and normal oral mucosa. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway conducted. Protein–protein interaction (PPI) network analysis was performed in the STRING database. CytoHubba in the Cytoscape software was applied to determining the top 10 hub genes, whose relative miRNA was identified through RNA Interactome Database. Overall, 627 DEGs was identified in OLP samples, including 351 highly expressed genes and 276 lowly expressed genes. GO analysis indicated that the epidermal differentiation was mostly enriched. For the KEGG pathway, the DEGs in OLP samples were mostly involved in Staphylococcus aureus infection. Top 10 hub genes were identified from the PPI network. The miRNA (hsa-miR-98-5p) was regarded as the mostly possible miRNA involved in OLP.

Conclusions The epidermal differentiation complex and functional miRNAs (hsa-miR-98-5p, hsa-let-7e-5p, hsa-let-7f-5p) were potential biomarkers of OLP

Clinical Relevance Of The Findings

Our results helped to identify the biomarkers of OLP including epidermal differentiation complex and functional miRNAs (hsa-miR-98-5p, hsa-let-7e-5p, hsa-let-7f-5p, etc).

Introduction

Oral lichen planus (OLP) was a common oral mucosal disease, and it was a chronic autoimmune disease.[1] The disease occurred more often in middle-aged people, with more women than men.[2] The typical lesions were characterized by small papules the size of a needle connected into white or off-white fine streaks, which were intertwined into a network, dendritic or ring shape.[3] Most of the lesions were symmetrical, with congestive erosion ulcers, and the most frequent site was the cheek.[4] Patients often had no symptoms. Some patients may feel rough mucous membranes, burning sensation and dry mouth, which affected eating and speech.[5] It had been observed that the incidence of OLP in the population was about 2%.[6] A recent meta-analysis showed that the incidence of OLP was different in different regions, with a slightly higher incidence in European population (1.43%) and a slightly lower incidence in Asian population (0.49%).[7] OLP might develop into malignant lesions and was classified as a premalignant condition by the World Health Organization.[3] However, the etiology and pathogenesis of OLP were still limited, and they were believed to be related to various factors, such as immune factors, mental factors, and infectious factors.[8]

Identification of biomarkers of oral lichen planus would help analyze the pathogenesis and influencing factors of different patients, and provide a basis for clinical personalized and precise treatment.[9] Changes in the expression of various genes were considered to be related to the occurrence of oral lichen planus.[10,11] But there was no biomarker that can be used as the gold standard. Therefore, there was still a need to explore reliable biomarkers.

In recent years, the development of gene microarray had provided a new perspective for studying the pathogenesis of diseases.[12] It could efficiently and quickly find abnormally expressed genes in diseased tissues and determine disease-related biomarkers.[13] As an emerging research method, clinical bioinformatics could identify abnormally expressed genes in diseased tissues by analyzing data obtained from high-throughput microarray and sequencing technology, which was considered to be one of the promising and key methods to help achieve early diagnosis and effective treatment.[14]

This study used bioinformatics methods to perform differential gene analysis and functional cluster analysis on OLP transcription microarray from public databases. Moreover, protein-protein interaction networks and related miRNA networks were established. The aim of this research was to identify the differentially expressed genes and their potentially interacting miRNAs in OLP to provide a possible explanation of the pathogenesis of OLP and therapeutic biomarkers.

Materials And Methods

Source of data

The OLP microarray dataset (GSE52130) was download from the GEO database through the GEO query package.[15] The dataset was based on GPL10558 Illumina HumanHT-12 V4.0 expression beadchip. Altogether 14 samples including 7 OLP samples and 7 normal oral epithelium samples were incorporated in this research.

Preprocessing of data

Bioconductor package (3.13 version) of R software (4.1.0) was used to preprocess the data. The probes corresponding to multiple molecules were removed. When various probes corresponded to the same molecule, only the probe with the largest signal value was reserved. Then the box diagram was conducted through ggplot2 (3.3.3 version) to estimate the standardization of the samples, and the clustering analysis between the OLP group and the normal group was conducted by umap package (0.2.7.0 version).

Differentially expressed genes analysis

Linear models were fitted by limma package of R software (4.1.0) to further determine the differential expressed genes (DEGs) between the OLP group and normal group.[16] DEGs were defined as genes with adjust P -value < 0.05 and $|\log_2(FC)| > 1.0$.

Functional enrichment analysis of DEGs

Gene Ontology (GO) database (<http://www.geneontology.org/>) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways (<https://www.genome.jp/kegg/>) were analyzed for the DEGs. P -value < 0.05 was indispensable for the GO/KEGG terms, which were determined as significantly enriched.

Protein–protein interaction (PPI) network analysis

STRING (<https://string-db.org/>), a database of known and predicted PPI, was applied to the identification of protein interactions. Cytoscape software (3.8.2 version) was used to visualize the PPI. In addition, CytoHubba, a plug-in of Cytoscape, was used to identify the top 10 hub genes through Maximal Clique Centrality algorithm.[17]

MiRNA network of top 10 hub genes

RNA Interactome Database (<http://www.rnainter.org/>) was screened for the relevant miRNAs of top 10 hub genes.[18] The interaction score should not be lower than 0.2. The top 30 relevant miRNAs were included. The miRNAs, targeting at least 3 hub genes, were identified.

Results

DEGs of OLP

The median of each sample was basically on a horizontal line, and it indicated that the degree of normalization between samples was good. (Figure 1A) The samples of each group are separated in the UMAP figure, showing that the difference between the groups was obvious. (Figure 1B) According to the definition of DEGs, a total of 627 DEGs was identified in OLP samples, including 351 highly expressed genes and 276 lowly expressed genes. (Figure 1C) The expression of top20 genes with high and low expression in the visualized expression heatmap. (Figure 1D)

Functional enrichment of DEGs

GO enrichment included the functional information of biological process (BP), molecular function (MF) and cellular component (CC), in which the DEGs were involved. For the BP, the DEGs in OLP samples were mostly associated with epidermis development, skin development, epidermal cell differentiation and keratinocyte differentiation. (Figure 2A) For the MF, the DEGs in OLP samples were mostly involved in enzyme inhibitor activity, peptidase regulator activity, endopeptidase regulator activity, peptidase inhibitor activity and endopeptidase inhibitor activity. (Figure 2B) For the CC, the DEGs in OLP samples were mostly related to cornified envelope, intermediate filament cytoskeleton and intermediate filament. (Figure 2C) For the KEGG pathway, the DEGs in OLP samples were mostly involved in *Staphylococcus aureus* infection, Estrogen signaling pathway, Serotonergic synapse and Histidine metabolism. (Figure 2D)

PPI network construction

STRING database was used for PPI analysis of DEGs, and further Cytoscape software was applied to analyze and visualize the results. (Figure 3A) Moreover, top 10 genes were identified as the possible hub genes by the CytoHubba, including LOR, LCE3D, LCE3E, LCE1B, LCE2B, SPRR2E, SPRR2G, LCE2A, RPTN and CDSN. (Figure 3B) The top 10 hub genes were all upregulated in OLP samples.

MiRNA network of top 10 hub genes

RNA Interactome Database was used for the establishment of the mRNA-miRNA interaction network. (Figure 4) For example, the miRNA (hsa-miR-98-5p) was found to interact with 5 hub genes (LOR, SPRR2G, LCE2B, CDSN and LCE2A). The miRNA (hsa-let-7e-5p, hsa-let-7f-5p, hsa-let-7d-5p, hsa-miR-135a-5p, hsa-miR-202-3p, hsa-miR-326, hsa-miR-708-5p, hsa-miR-330-5p, hsa-miR-28-5p) was found to interact with 3 different hub genes. (Figure 5)

Discussion

OLP was a common oral mucosal disease. However, the pathogenesis of OLP was unclear, and it was believed to be related to various factors. Notably, there was still a lack of effective treatment for OLP. The molecular mechanisms of OLP remained to be investigated for further identifying the potentially effective therapeutic targets. Bioinformatics was one of the promising methods to find the abnormally expressed genes for further identification of therapeutic targets. In this research, we used a gene series of OLP from GEO database to find 627 DEGs was identified in OLP samples, including 351 highly expressed genes and 276 lowly expressed genes. Functional enrichment analysis found the DEGs enrich in epidermis development and enzyme inhibitor activity. The function of hub genes was almost related to the cornified cell envelope formation and epidermal barrier integrity.[19-21]

Loricrin cornified envelope precursor protein (LOR) encoded loricrin, which was one of major proteins in the envelope of terminally differentiated epidermal keratinocytes.[22] Mutations in LOR were related to

Vohwinkel syndrome, which was defined as palmoplantar keratoderma.[23] LOR had been found to be associated with cornified cell envelope formation, which resulted in keratinization in the OLP lesions.[20] It was consistent with our results. However, another study had indicated that loricrin was not detected in OLP samples through immunohistochemical technique.[24] Whether LOR could be regarded as a biomarker for OLP needed more researches.

Late cornified envelope (LCE) family included multiple genes, which encoded stratum-corneum proteins.[25] LCE genes had been found to be important in skin and upregulate under the UV light.[20] They were the precursors of the cornified envelope of the stratum corneum.[26] Therefore, they participated in the keratinization pathway, which was involved in the pathology of OLP.[27] Moreover, LCE proteins were identified with antimicrobial activator to be closely connected with the innate host defense, indicating their potential function in the pathogenesis of OLP.[28] The LCE genes not only correlate to keratinization, but also involved the immune response, both of which were the possibly major etiology of OLP. Nevertheless, up to now, few studies focused on the function of LCE in the development of OLP.

Small proline rich protein (SPRR) genes encoded small proline rich proteins, which participated the epidermal differentiation complex to further constitutes the cornified cell envelope.[29] In addition, repetin (RPTN) gene, belonging to S100 protein family, was also involved in the cornified cell envelope formation. The LOR, LCE, SPRR and RPTN were parts of human epidermal differentiation complex (EDC).[20] The GO analysis in this study enriched the epidermal differentiation. It was indicated that upregulated or activated EDC might play a role in the pathogenesis of OLP, and the LOR, LCE, SPRR and RPTN could be further investigated.

Another bioinformatic study had indicated that high expression of filaggrin (FLG) gene was related to hyperkeratosis, and ALOX12B gene could aggravate wound in the oral mucosa.[30] Moreover, FLG and ALOX12B were found to be involved in OLP.[31] FRAS1 gene was indicated to be related to separation between lamina propria and epithelium in a bioinformatic research.[31] The identified hub genes of OLP in previous studies were different from that in our study.[9,10] More basic researches and clinical researches were urged to prove the function of these genes in the pathogenesis of OLP.

MiRNA was a kind of endogenous non-coding RNA, extensively participating in gene post-transcriptional regulation activities.[32] MiRNA could inhibit target gene expression at protein translation level and induce the degradation of target mRNA.[33] MiR-164a and miR-21 were found to be upregulated over 2-fold in the OLP samples.[34] MiR-155 targeted suppressor of cytokine signaling 1 (SOCS1) to relieve the inhibition of phosphorylated janus kinase (JAK), then signal transducer and activator of transcription (STAT) was activated to M1 polarization and Treg differentiation, which might be involved in the pathogenesis of OLP.[35] In the present study, the miRNAs related to the hub genes remained to be investigated.

Our study provided a new direction for mechanism research of OLP. The role of EDC relevant genes and corresponding miRNAs in OLP remained to be studied. Nonetheless, there were some limitations in the present research. (1) The function of hub genes and miRNAs in OLP was less studied; (2) The interaction

between hub genes and miRNAs was not investigated. However, the results of this research were still meaningful, as potential biomarkers for diagnosis and treatment of OLP were provided.

Conclusions

Compared to the normal oral mucosa, genes, including LOR, LCE3D, LCE3E, LCE1B, LCE2B, SPRR2E, SPRR2G, LCE2A, RPTN and CDSN, were significantly highly expressed in OLP samples. These genes were parts of the EDC, referring to the potential role of EDC in the pathogenesis of OLP. Possibly functional miRNAs (hsa-miR-98-5p, hsa-let-7e-5p, hsa-let-7f-5p, etc) were also identified. Our results might help to identify the biomarkers of OLP. However, more basic and clinical experiments were needed to validate the role of above molecules in OLP.

Declarations

Conflicts of interests

No conflict of interest was involved in the present research. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Figures

Figure 2

Significantly enriched GO terms and KEGG pathways. (A) Enriched biological process; (B) Enriched molecular function; (C) Enriched cellular component; (D) Enriched KEGG pathways.

Figure 3

The network of protein-protein interaction and top 10 hub genes. (A) Protein-protein interaction of the differentially expressed genes; (B) The top 10 hub genes identified through CytoHubba.

Figure 4

MiRNA network of top 10 hub genes.

Figure 5

The collective interaction between the genes and miRNAs.