JBUON 2018; 23(6): 1662-1670
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Biological information analysis of differentially expressed genes in oral squamous cell carcinoma tissues in GEO database

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Summary

Purpose: *This study aimed to detect the differentially expressed genes between oral squamous cell carcinoma (OSCC) tissues and adjacent normal tissues, and perform pathway analysis and protein-protein interaction (PPI) analysis on differentially expressed genes (DEGs).*

Methods: *Gene Expression Omnibus (GEO) database related to human tumors was selected from the National Center for Biotechnology Information (NCBI), and GSE31056 and GSE3524, two microarrays containing OSCC gene expression data, were extracted from it. Analysis of differentially expressed genes in the two microarrays was performed using "R" software, and the volcanic map was drawn. Then, Venn diagram was used to integrate the differentially expressed genes screened out by the two microarrays, and PPI [Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG)] analysis of DEGs after integration was performed using Cytoscape, DAVID, STRING and KOBAS. A total of 207 differentially expressed genes were screened out by the two microarrays. 103 proteins encoded by differentially expressed genes screened out by STRING software had interaction. The expression network of differentially expressed genes was constructed, and some proteins, closely related to other proteins such as STAT1, were screened out by Cytoscape software*

Results: *GO analysis and KEGG analysis found that the differentially expressed genes were mainly enriched in "extracellular region", "extracellular region part" and "membrane-bound vesicle", and mainly involved in biological processes such as "Amoebiasis", "Glycerolipid metabolism" and "Arachidonic acid metabolism". In this study, 207 differentially expressed genes were successfully screened out from the two OSCC microarrays. PPI, GO and KEGG pathways of 103 interacting proteins were successfully constructed. Key genes were screened out, annotation and pathway analysis of which were performed.*

Conclusion: *This study was helpful to further study the relationship between OSCC gene directions.*

Key words: *oral squamous cell carcinoma, differentially expressed gene, GO enrichment, KEGG pathway analysis, protein-protein interaction*

Introduction

OSCC is the most common type of oral cavity tumor, accounting for 90% of the cases, and the number of new cases worldwide is approximately 650,000 annually, ranking eighth among the malignant tumors in the world [1]. From the report by Hasegawa et al. [2], it is rather clear that there is a trend of younger age among OSCC patients. In recent years, the number of cases has increased, and the 5-year overall survival rate has decreased from less than 50% to less than 30%. The statistics warn us from the side that studies on OSCC prevention, diagnosis and treatment need to be enhanced. The low survival rate of OSCC is mainly due to cervical lymph node metastasis

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Received: 02/06/2018; Accepted: 19/06/2018

at the time of diagnosis, and the prognosis is often poor in this group of patients [3]. In the study of Xiao et al. [4], the expression of Bit-1 mRNA and its protein, which is related to the occurrence, metastasis and invasion of OSCC, may be a key factor in OSCC invasion and metastasis, and helpful for the clinical diagnosis of OSCC, expected to be a potential target for OSCC molecular therapy. The study of OSCC has gone deep into the molecular angle, but no optimal target has been found yet.

In recent years, the development of bioinformatics has made great progress at the molecular level of multiple tumors such as gastric cancer, colon cancer and pancreatic cancer [5]. It has been a new research hotspot deep delving gene expression profile data using bioinformatics at present. Gene Expression Omnibus (GEO) database is the gene expression assembler of the National Center for Biotechnology Information (NCBI) of the United States containing the gene microarray expression profile of a variety of diseases, which is a common database for bioinformatics analysis at present [6]. Therefore, we intended to find genes having an effect on OSCC using bioinformatics to expand the current study results in this direction.

Methods

This study was approved by the Ethics Committee of Sichuan University, Chengdu, Sichuan 610041, P.R China.

Acquisition of gene data expression profile

GEO database of NCBI (https://www.ncbi.nlm.nih.gov) was logged in, the OSCC search format was edited, and the GSE3524 and GSE31056 datasets related to OSCC gene expression profile were acquired. There were 16 tumor tissue samples and 4 normal tissue samples in GSE3524 microarray; 22 tumor tissue samples and 23 normal tissue samples in GSE31056 microarray. Specific information is shown in Table 1.

Preprocessing of raw data and screening of differentially expressed genes and volcanic map

Statistical analysis of microarray data was performed using the The R Project for Statistical Computing software (SAS/SAIS software Co, United States), preprocessing of microarray data was performed using JustRMA algorithm, and filtration and standardization of data was performed using the median method. Requirements for gene filtration: 1) the gene median of the two types of samples changed at least 2-fold, and this change was not less than 20% of the sample size; 2) the number of deletions of gene expression data was not more than 50%. Two independent t-tests were performed on genes passing the filtration criteria. Classification and comparison of samples on dataset was performed using Class comparison tool and the differential expression genes between OSCC and normal samples were found and the volcanic map was drawn.

Screening of common differentially expressed genes

Venn diagram analysis of differentially expressed genes screened out by two microarrays was performed. The genes co-existing in differentially expressed genes in the two microarrays were defined as common differentially expressed genes and their expression amount in each microarray was preserved for subsequent analysis.

GO enrichment analysis and KEGG pathway analysis

GO enrichment analysis and KEGG pathway analysis of differentially expressed genes after integration were performed using DAVID (Database for Annotation, Visualization and Integration Discovery) and "Bingo" plug-in of Cytoscape software. First, the DAVID database (https://david.ncifcrf.gov/) was logged in, the function of Gene ID Conversion was selected, and the list of differentially expressed genes was submitted. Then, the OFFICIAL_GENE_SYMBOL was selected in the Select

Identifier, and the Gene List in List Type was selected. Finally, the Submit List was clicked.

GO enrichment analysis was performed using Cytoscape software. First, Cytoscape software (http://www.cytoscape.org/) was downloaded, the BINGO

Table 1. Information of GSE3524 microarray and GSE31056 microarray

Data	*GSE3524*	*GSE31056*
Platform	GPL96	GPL10526
Sample type	Tissue	Tissue
Disease	OSCC	OSCC
Object of study	Human beings	Human beings
Microarray providing mechanism	Center for Applied Genomics, Center for Human and Molecular Genetics,UMDNJ-NJ Medical School	Biostatistics, Harvard School of PublicHealth
Address	225 Warren Street W410Q,Newark,USA	655 Huntington Avenue, Boston,USA
Number of samples (use/total)	20/20	45/96
Microarray upload time	Oct 28, 2005	Jul 29, 2011
Microarray final update time	Dec 27, 2017	Oct 16, 2012

plug-in of Apps was opened after installation, the differentially expressed genes were input and Select ontology file was adjusted to GO Full, and Select organism/annotation was adjusted to Homo Sapiens. Then, the enrichment analysis was performed by clicking on Start BINGO.

Protein-protein interaction (PPI) analysis

PPI analysis of differentially expressed genes was performed using STRING software. PPI referred to the process of forming a protein complex by two or more protein molecules passing through a non-covalent bond. The STRING official website (https://string-db.org/)

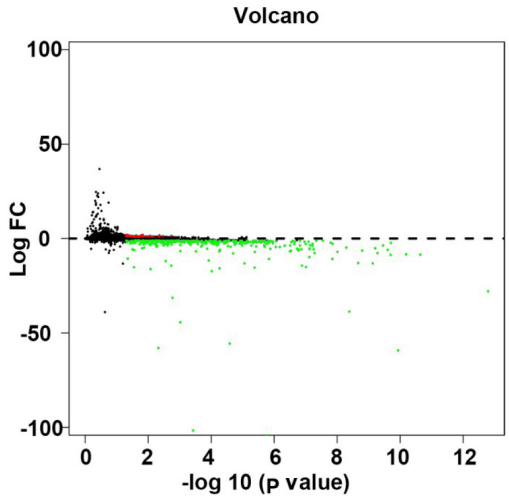

Figure 1. Volcanic Map of GSE3524. The volcanic map showed that in GSE3524 microarray, the up-regulated genes in OSCC tissues were significantly more than the down-regulated genes when compared to normal tissues, and the difference was more significant.

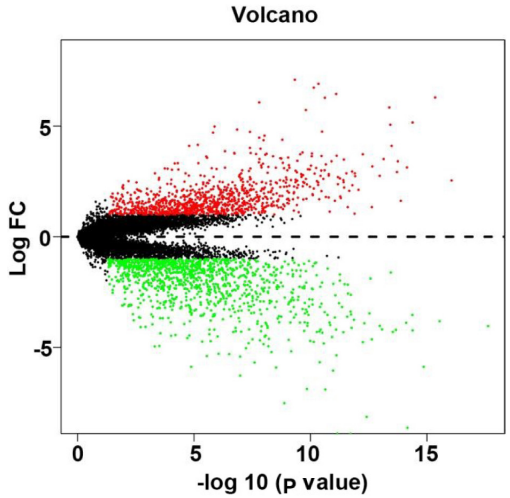

Figure 2. Volcanic Map of GSE31056. The volcanic map showed that in GSE31056 microarray, the number of down-regulated genes and that of up-regulated genes in OCSS tissues were similar, but the change of down-regulated genes was more obvious than that of up-regulated genes.

Table 2. Some of the major differentially expressed genes of GSE3524

Gene	*logFC*	*p value*	*adjusted p value*
TGM3	-27.93342961	1.61E-13	1.54E-09
COBL	-8.516995806	2.31E-11	1.10E-07
TGM1	-8.401868318	6.46E-11	2.05E-07
ENDOU	-59.29992732	1.17E-10	2.78E-07
ELL3	-2.311974842	1.97E-10	3.20E-07
TPPP3	-8.619783307	2.02E-10	3.20E-07
TYRP1	-5.990552083	2.53E-10	3.44E-07
DUOX1	-3.638025703	3.52E-10	4.19E-07
CYP2C18	-7.692976718	5.25E-10	5.56E-07
KLF8	-5.141737593	6.14E-10	5.85E-07

Table 3. Some of the major differentially expressed genes of GSE31056

Gene	*logFC*	*p value*	*adjusted p value*
SLC27A6	-4.039229618	2.36E-18	4.13E-14
PTK7	2.548701262	8.82E-17	7.71E-13
EPHX2	-3.820143764	2.86E-16	1.67E-12
PTHLH	6.290591247	4.47E-16	1.95E-12
FAM3B	-5.875283176	1.39E-15	4.84E-12
INHBA	5.16155721	4.16E-15	9.15E-12
FAM107A	-4.228824389	4.17E-15	9.15E-12
TCEAL2	-3.527906966	4.19E-15	9.15E-12
TMPRSS11B	-8.628706449	6.80E-15	1.25E-11
PMEPA1	3.130009194	7.19E-15	1.25E-11

was logged in, the list of differentially expressed genes was submitted under the option of multiple proteins, Homo sapiens was selected under the option of Organism, and SEARCH was clicked after completion.

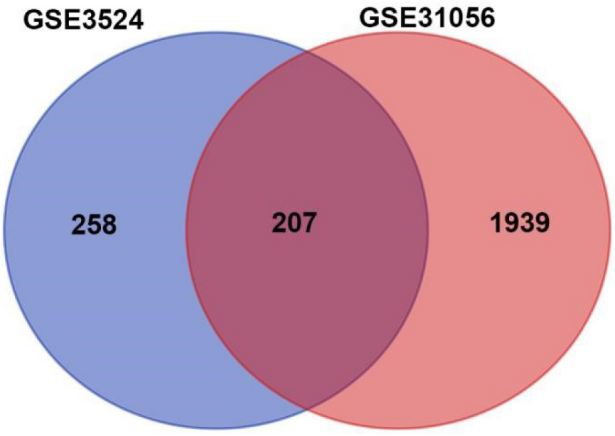

Figure 3. Venn diagram of common differentially expressed genes. The Venn diagram showed that there were 207 common differentially expressed genes between the two microarrays.

Results

Results of GSE3524 difference analysis

465 genes expressed differentially from normal tissues were screened out from GSE3524, among which 72 genes were up-regulated and 393 genes were down-regulated ($p<0.05$, fold change>2) in OSCC tissues. Some of the major differentially expressed genes are shown in Table 2. At the same time, the volcanic map was drawn, as shown in Figure 1.

Results of GSE31056 difference analysis

2146 genes expressed differentially from normal tissues were screened out from GSE31056, among which 991 genes were up-regulated and 1155 genes were down-regulated ($p<0.05$, fold change>2) in OSCC tissues. Some of the major differentially expressed genes are shown in Table 3. At the same time, the volcanic map was drawn, as shown in Figure 2.

Table 4. The first 10 common differentially expressed genes sequenced by p value in GSE3524

Gene	*GSE3524*			*GSE31056*		
	logFC	*p value*	*adjusted p value*	*logFC*	*p value*	*adjusted p value*
TGM3	-27.93342961	1.61E-13	1.54E-09	-6.873273926	1.42E-10	1.71E-08
COBL	-8.516995806	2.31E-11	1.10E-07	-1.07619624	0.000722001	0.003883889
TGM1	-8.401868318	6.46E-11	2.05E-07	-3.728134136	5.66E-07	1.12E-05
ENDOU	-59.29992732	1.17E-10	2.78E-07	-5.351312451	7.76E-12	1.92E-09
ELL3	-2.311974842	1.97E-10	3.20E-07	-1.921102273	1.07E-08	4.85E-07
TPPP3	-8.619783307	2.02E-10	3.20E-07	-1.233799905	0.038088512	0.099863086
TYRP1	-5.990552083	2.53E-10	3.44E-07	-3.939246787	2.60E-05	0.000248723
DUOX1	-3.638025703	3.52E-10	4.19E-07	-2.837588465	2.04E-08	8.13E-07
CYP2C18	-7.692976718	5.25E-10	5.56E-07	-3.889378529	8.43E-09	4.12E-07
HOPX	-13.06439725	7.44E-10	6.44E-07	-3.177179103	5.22E-10	4.54E-08

Table 5. The first 10 common differentially expressed genes sequenced by p value in GSE31056

Gene	*GSE31056*			*GSE3524*		
	logFC	*p value*	*adjusted p value*	*logFC*	*p value*	*adjusted p value*
SLC27A6	-4.039229618	-14.57471644	2.36E-18	-2.97367662	1.42E-10	1.71E-08
FCER1A	-4.205074744	2.17E-14	2.53E-11	-1.776940749	0.0003405	0.011851209
HLF	-4.300862248	2.90E-14	3.17E-11	-1.578876521	0.004316051	0.064068485
MAL	-8.134560474	3.89E-13	2.27E-10	-55.638558	2.59E-05	0.001687425
CYP3A5	-4.752839802	5.69E-13	3.03E-10	-5.442963006	0.000133891	0.005773656
CRNN	-8.884938809	1.96E-12	7.61E-10	-104.1212291	1.71E-06	0.000236612
EMP1	-2.13716606	3.46E-12	1.16E-09	-3.712051704	5.27E-06	0.00053975
KRT4	-8.882216207	6.95E-12	1.79E-09	-31.4339172	0.00169356	0.03602596
ENDOU	-5.351312451	7.76E-12	1.92E-09	-59.29992732	1.17E-10	2.78E-07
PLP1	-4.199974454	7.92E-12	1.92E-09	-1.79301662	0.005027502	0.070019549

Screening of common differentially expressed genes between GSE3524 and GSE31056

207 common differentially expressed genes between GSE3524 and GSE31056 were screened out using Venn diagram analysis, as shown in Figure 3. P values in different microarrays were regarded as the standard sequence, and 10 common differentially expressed genes with the lowest p value in GSE3524 (Table 4) and in GSE31056 (Table 5) were listed respectively.

GO enrichment analysis of common differentially expressed genes

GO enrichment analysis of 207 common differentially expressed genes between GSE3524 and GSE31056 was performed using DAVID and

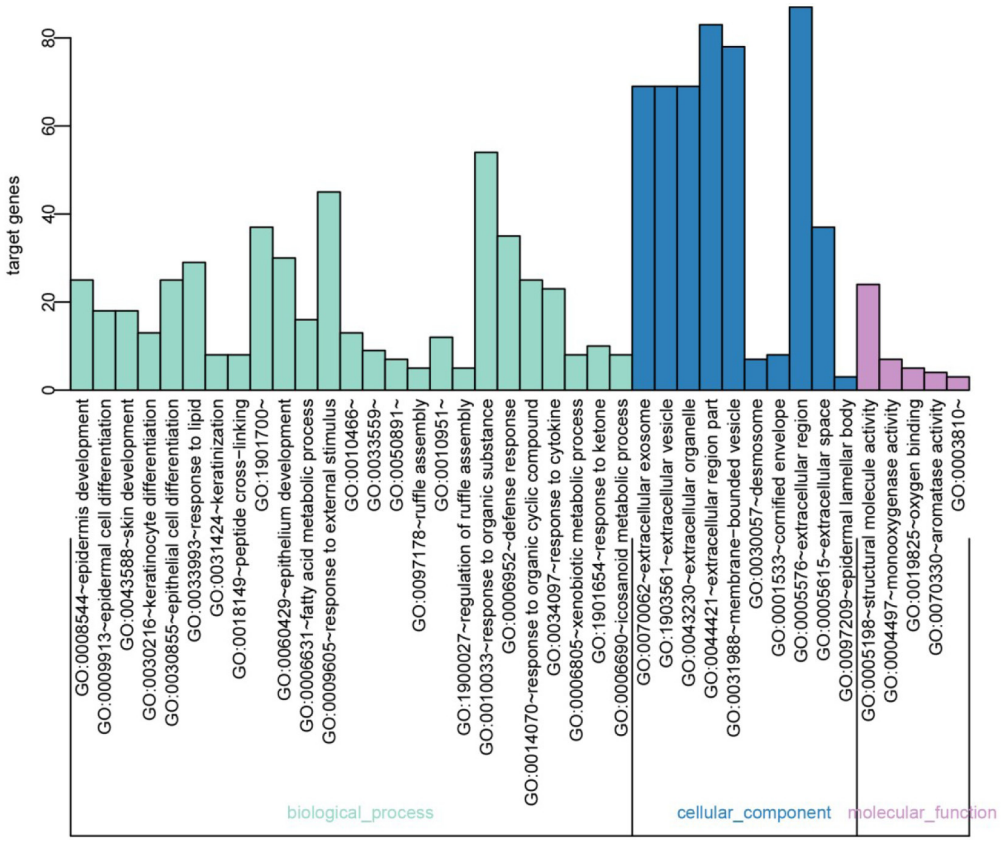

Figure 4. GO enrichment analysis of common differentially expressed genes. The horizontal coordinate was enriched GO and the vertical coordinate was the number of differentially expressed genes. Different colors represented different GO classifications, namely, Molecular function, Biological process and Cellular component. In this map, the genes enriched by cellular component classification were more and mainly concentrated in "extracellular region", "extracellular region part" and "membrane-bounded vesicle".

Table 6. Results of KEGG pathway analysis of common differentially expressed genes

Term	*Count*	*p value*	*FDR**
hsa05146:Amoebiasis	6	0.007090344	8.023578776
hsa00561:Glycerolipid metabolism	4	0.028304201	28.64418302
hsa00590:Arachidonic acid metabolism	4	0.033591254	33.07656875
hsa00982:Drug metabolism - cytochrome P450	4	0.042415773	39.91706166
hsa05140:Leishmaniasis	4	0.047223037	43.36829191
hsa05164:Influenza A	6	0.048387946	44.17682705
hsa00980:Metabolism of xenobiotics by cytochrome P450	4	0.052287927	46.80746235
hsa05168:Herpes simplex infection	6	0.057756263	50.30522973
hsa00350:Tyrosine metabolism	3	0.060242361	51.82474512
hsa05204:Chemical carcinogenesis	4	0.063169879	53.55949802
hsa05162:Measles	5	0.06530991	54.79124161

*false discovery rate

Cytoscape, suggesting that the differentially expressed genes were mainly enriched in "extracellular region", "extracellular region part" and "membrane-bounded vesicle" in "cellular component", which may focus on affecting extracellular matrix protein, as shown in Figure 4.

KEGG pathway analysis of common differentially expressed genes

KEGG pathway analysis of 207 common differentially expressed genes between GSE3524 and GSE31056 was performed using KOBAS3.0 system, and 11 KEGG pathways were found, of which the top 6 were "Amoebiasis", "Glycerolipid metabolism", "Arachidonic acid metabolism", "Drug metabolism-cytochrome P450", "Leishmaniasis" and "Influenza A", respectively. Eleven specific KEGG pathways are shown in Table 6.

PPI analysis of common differentially expressed genes

Analysis of 207 common differentially expressed genes between the two microarrays was performed using STRING, suggesting that 103 proteins were found to interact with each other, among which the first 10 proteins with more connect in nodes were "STAT1", "OAS2", "IVL", "TLR2", "IFIH1", "IFIT1", "IFI44L", "IFI6", "RSAD2" and "RTP4". STAT1 was the most important one, connecting a total of 18 proteins, as shown in Figures 5 and 6.

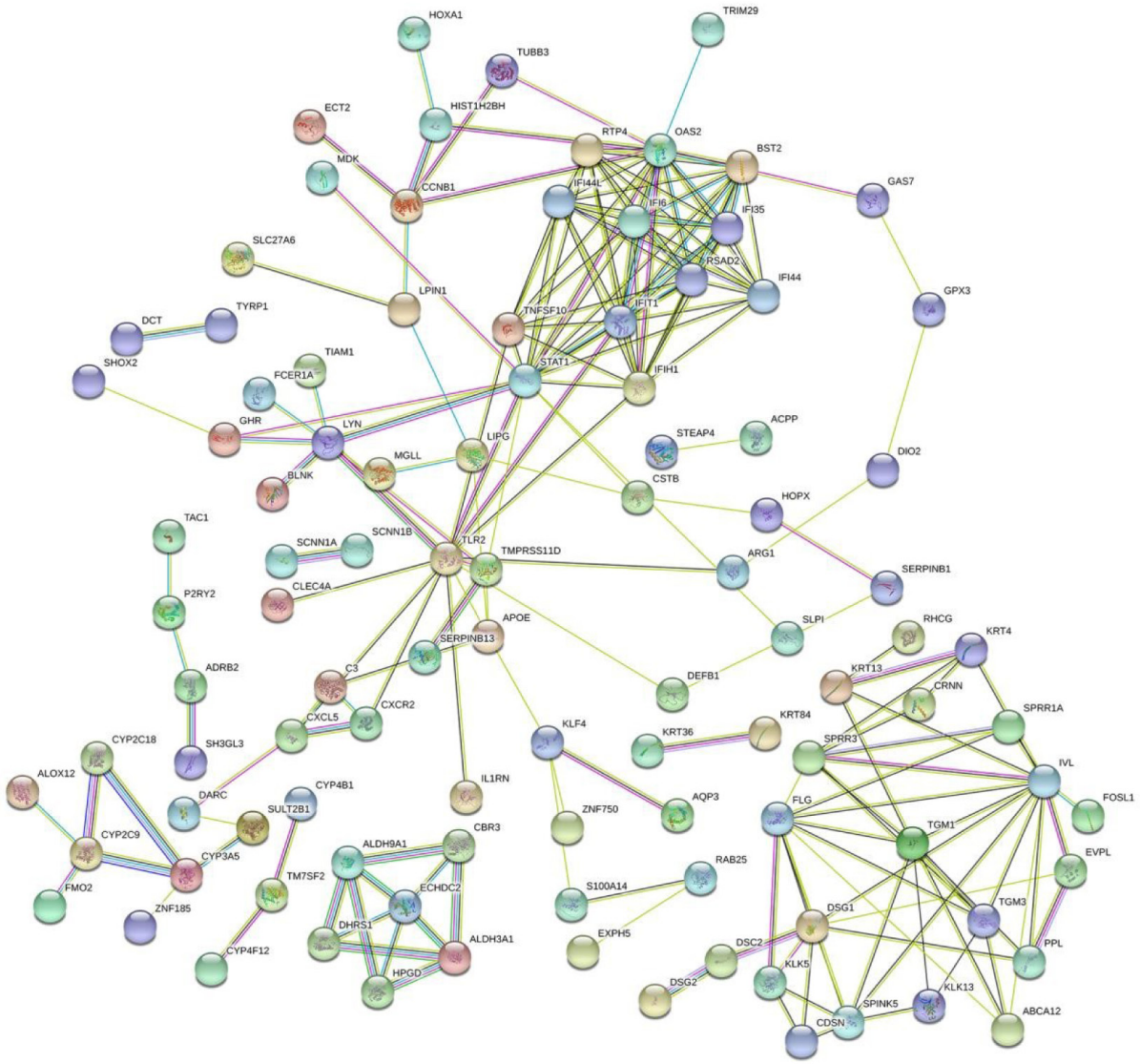

Figure 5. PPI analysis diagram of common differentially expressed genes. The circles represent the gene, the lines represent the protein interaction between genes, and the result inside the circles represent the protein structure. The color of the thread represents different evidence of protein interaction. (small nodes: protein of unknown 3D structure; large nodes: some 3D structure is known or predicted; A red line indicates the presence of fusion evidence ; a green line-neighborhood evidence; a blue line-coocurrence evidence; a purple line-experimental evidence; a yellow line–text mining evidence; a light blue line-database evidence; a black line-coexpression evidence).

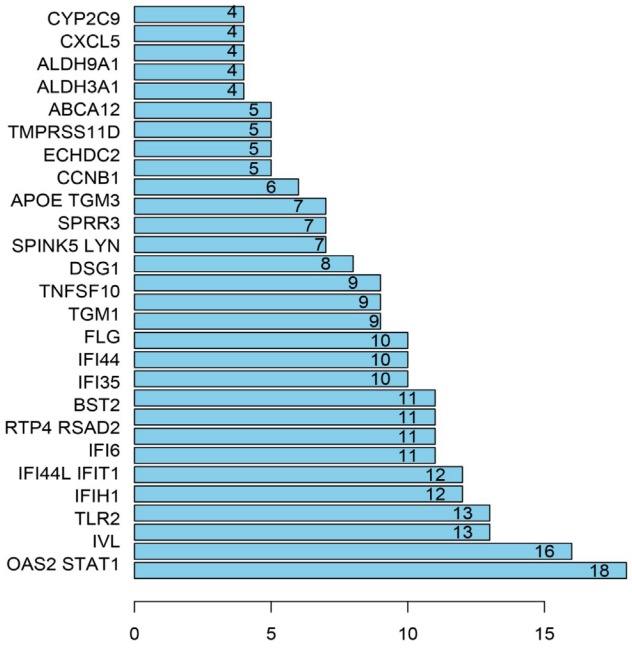

Figure 6. PPI analysis of core protein histogram. The vertical coordinate shows the name of the gene, the horizontal coordinate shows the number of adjacent genes, and the height represents the number of genetic lines. The diagram showed that a total of 18 proteins were linked to STAT1, ranking first in the number of connexins.

Discussion

At present, the tumor markers commonly used in OSCC diagnosis have been criticized because of their low sensitivity and specificity. The diagnosis is mainly based on imaging methods, but most patients have been in the late period when diagnosed as OSCC by imaging methods [7,8]. For treatment, common methods are traditional surgery, radiotherapy and chemotherapy, and the trauma of the traditional surgical treatment to the patient was greater [9,10]. According to the statistics of Chaves et al. [11], about 20% of OSCC patients treated by traditional surgical treatment still develop recurrence. At present, radiotherapy and chemotherapy are also commonly used for cancer treatment, but the immune function of the patient is more severe, making the patient susceptible to other diseases during the recovery from treatment [12]. The molecular targeted therapy has not been further used in OSCC, so our intention was to expand the study results of OSCC relevant genes through this study, providing help for the clinical diagnosis and treatment of OSCC in the future.

In this study, several important components in bioinformatics combining computer science with biological science were used to make the exploration of differentially expressed genes more concise and clear. Public databases were used to make the time, resource, manpower previously used for molecular studies more efficient.

Two microarrays related to OSCC tissues were obtained from GEO database. 465 and 2146 differentially expressed genes were screened out from GSE3524 and GSE31056 respectively using R software, and there were 207 common differentially expressed genes between the two microarrays. Subsequent GO enrichment analysis and KEGG pathway analysis showed that the differentially expressed genes in OSCC tissues were mainly distributed in "extracellular region" and "membrane-bound vesicles" and involved in "Amoebiasis", "Glycerolipid metabolism" and other biological processes and signal pathways, suggesting that the occurrence and development of OSCC may be related to extracellular matrix protein variation, infectious diseases and fatty acid synthesis. In this study, ENDOU, which was enriched in extracellular matrix , was the gene with significant difference between the two microarrays, and the change of protein in extracellular matrix often affected the development of tumor [13]. van der Windt et al. [14] proposed that the change of neutrophil extracellular matrix promoted the development of hepatocellular carcinoma in patients with non-alcoholic fatty hepatitis. There were few studies on the extracellular matrix protein ENDOU, so further annotation and discussion of this protein was needed. In the study of Lindemann et al. [15], the cellular structure of oral cells changed abnormally, closely related to the incidence of OSCC. The proliferation of tumor cells required cells to constantly provide endogenous synthetic fatty acids, provide raw materials for cell membrane phospholipids or acylation of cell proteins, ultimately affecting the biological behavior of tumors [16,17]. In the report of Naqvi et al. [18], the fatty acid synthesis level in OSCC fresh samples was significantly higher than that in adjacent normal tissues and other maxillofacial tissues. In the subsequent PPI analysis, we found that proteins such as "STAT1", "OAS2" and "IVL" all had strong interactions, suggesting that these proteins may have a greater impact on the occurrence and development of OSCC, resulting from the side that they were expected to be good markers for the diagnosis and treatment of OSCC in the future. In the study of Mori et al. [19], immunostaining analysis of 30 patients with oral precancerous lesions was performed, the results of which showed that STAT1 was widely distributed in the lesion tissues. STAT1 was also involved in the study of Qu et al. [20]. It was found that STAT1 had a promotive effect on the proliferation and invasion of nasopharyngeal carcinoma cell line cne-2r, and a better radiotherapy effect could be obtained by inhibiting the expression of STAT1. In the report of Wu

et al. [21]], the relevant information of OSCC and STAT1 was found, which could predict the development and prognosis of OSCC through STAT1/ATF4/S100P/p65 signal transduction pathway, thus helpful to broaden the anti-tumor treatment methods of OSCC. The changes of STAT1 in different specimen types of OSCC patients needed to be further explored. OAS2 was found to be associated with hepatitis C virus [22] and studies on tumor-related diseases have not yet been conducted. Mahale et al. [23] mentioned that hepatitis C virus was associated with OSCC, so attention to this protein should be paid and further study may be needed to link it to OSCC. By partial Gene retrieval in NCBI, we found that IVL was located in Chromosome 1, NC_000001.11 (152908563..152911886). There were few reports on this protein, but in this study it was found that it belongs to the common differentially expressed genes between the two microarrays related to OSCC tissues. A total of 13 proteins were linked in PPI analysis, which need to be further explored in the future.

The biggest drawback in this study is the included sample size, location, and microarray release time. The time between uploading the two microarrays is several years apart, and the sequencing methods and experimental conditions may be different. There is a certain error, but the common differentially expressed genes can also be screened out in different sequencing methods and experimental conditions, suggesting indirectly that these most important proteins may have a significant impact on OSCC and need to be further studied.

After a long time of calculation and discussion, we finally determine that OSCC is closely related to extracellular matrix protein variation, fatty acid synthesis and metabolism and STAT1, OAS2. We will develop more in-depth study on these aspects under the condition of permission. Few studies have been made on the tumor markers and molecular targeting of OSCC. We hope that the results of this experiment can enrich the study in this aspect and provide help for clinical diagnosis and treatment in the future.

Authors' contributions

LZ and YW were responsible for Preprocessing of Raw Data and Screening of Differentially Expressed Genes and Volcanic Map. HF were mainly devoted on Screening of Common Differentially Expressed Genes. HY helped with Protein-protein Interaction (PPI) Analysis. All authors read and approved the final manuscript.

Conflict of interests

The authors declare no conflict of interests.

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