Identification of Key Genes and Biological Pathways in Lung Adenocarcinoma by Integrated Bioinformatics Analysis

Lung Adenocarcinoma and Integrated Bioinformatics Analysis

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Abstract

BACKGROUND
The objectives of this study were to identify hub genes and biological pathways involved in lung adenocarcinoma (LUAD) via bioinformatics analysis, and investigate potential therapeutic targets.

AIM
To determine reliable prognostic biomarkers for early diagnosis and treatment of LUAD.

METHODS
To identify potential therapeutic targets for LUAD, two microarray datasets derived from the Gene Expression Omnibus (GEO) database were analyzed, GSE3116959 and GSE118370. Differentially expressed genes (DEGs) in LUAD and normal tissues were identified using the GEO2R tool. The Hiplot database was then used to generate a volcanic map of the DEGS. Weighted gene co-expression network analysis was conducted to cluster the genes in GSE116959 and GSE118370 into different modules, and identify immune genes shared between them. A protein–protein interaction network was established using the Search Tool for the Retrieval of Interacting Genes database, then the CytoNCA and CytoHubba components of Cytoscape software were used to visualize the genes. Hub genes with high scores and
co-expression were identified, and the Database for Annotation, Visualization and Integrated Discovery was used to perform enrichment analysis of these genes. The diagnostic and prognostic values of the hub genes were calculated using receiver operating characteristic curves and Kaplan-Meier survival analysis, and gene-set enrichment analysis was conducted. The University of Alabama at Birmingham Cancer data analysis portal (UALCAN) was used to analyze relationships between the hub genes and normal specimens, as well as their expression during tumor progression. Lastly, validation of protein expression was conducted on the identified hub genes via the Human Protein Atlas database.

RESULTS
Three hub genes with high connectivity were identified; cellular retinoic acid binding protein 2 (CRABP2), matrix metallopeptidase 12 (MMP12), and DNA topoisomerase II alpha (TOP2A). High expression of these genes was associated with a poor LUAD prognosis, and the genes exhibited high diagnostic value.

CONCLUSION
Expression levels of CRABP2, MMP12, and TOP2A in LUAD were higher than those in normal lung tissue. This observation has diagnostic value, and is linked to poor LUAD prognosis. These genes may be biomarkers and therapeutic targets in LUAD, but further research is warranted to investigate their usefulness in these respects.

Key Words: CRABP2, expression profiling data, hub genes, lung adenocarcinoma, MMP12, TOP2A

**Core Tip:** Lung cancer is an important cause of cancer-related death worldwide. This study conducted multiple bioinformatics analysis methods to explore potential therapeutic targets for LUAD. Finally, three hub genes with high connectivity were identified, namely cellular retinoic acid binding protein 2 (CRABP2), matrix metallopeptidase 12 (MMP12), and DNA topoisomerase II alpha (TOP2A). High expression of these genes was associated with a poor LUAD prognosis, and the genes exhibited high diagnostic value. Therefore, these genes may be biomarkers and therapeutic targets for LUAD.

**INTRODUCTION**

Lung cancer is an important cause of cancer-related death worldwide, with incidence and mortality rates of 11.6% and 18.4%, respectively. Non-small cell lung cancer is the most common type of lung cancer, and lung adenocarcinoma (LUAD) is the main histological subtype of non-small cell lung cancer. Most cases of LUAD are diagnosed at an advanced or metastatic stage; in addition, the 5-year survival rate is extremely low. Currently, treatment effectiveness for advanced LUAD is limited. Moreover, LUAD is associated with a high risk of recurrence after treatment due to the heterogeneity of tumors. Therefore, it is imperative to identify a reliable prognostic biomarker for early diagnosis and treatment. The use of such biomarkers could potentially improve the prognosis of patients with lung cancer.

The gene chip is a systematic high-throughput method for detecting and analyzing differentially expressed genes (DEGs) in various tissues. This technique can assist in the identification of prognostic genes and biomarkers.
of cancer [8-10]. Thus, it has become a powerful tool for studying the
differential expression of genes related to the carcinogenesis and progression
of LUAD. In addition, it provides the possibility to analyze the tumor
microenvironment and the functional diversity of tumor-infiltrating immune
cells [11-13]. With the rapid development and application of gene chip
technology, researchers have accumulated a large amount of gene data.
Hence, gene mining based on these data has become a research hotspot [14]. In
this study, various bioinformatics methods were utilized to identify the core
genes associated with the prognosis of LUAD. These core genes can be used
for disease diagnosis and prognosis, and may help elucidate the mechanisms
underlying LUAD.

MATERIALS AND METHODS

Microarray Data

The National Center for Biotechnology Information-Gene Expression
Omnibus (NCBI-GEO) is a public database
Adenocarcinoma” and “Homo Sapiens” in our search, we obtained two
datasets, GSE116959 (including 57 LUAD tissues and 11 normal tissues) and
GSE18370 (including 6 LUAD and 6 normal tissues). These datasets were
downloaded and analyzed using GEO2R.

Identification of DEGs and Data Visualization

We analyzed DEGs between LUAD and normal tissues in the GSE116959 and
GSE18370 datasets using the GEO2R tool
diagrams drawn for each dataset were obtained from the Hiplot database [15]
(https://hiplot-academic.com/).

Weighted Gene Co-expression Network Analysis (WGCNA)
WGCNA is a systems biology method that can interconnect and cluster different types of genes into various modules to calculate the correlation between genes and clinical practice [16]. The online tool EHBIO platform (http://www.ehbio.com/Cloud_Platform/front/#/) was used to perform WGCNA on the GSE116959 and GSE118370 datasets. After screening, modules that were more relevant to the sample characteristics were included in subsequent analyses.

Gene Ontology (GO) Enrichment Analysis of DEGs

Database for Annotation, Visualization and Integrated Discovery (DAVID) [17] is a web server for gene lists, functional enrichment analysis, and functional annotation (https://david.ncifcrf.gov/). The latest version of the DAVID database (version 7.0) was used to conduct GO enrichment analyses of the DEGs.

Protein-Protein Interaction (PPI) Network Construction and Hub Gene Identification

The Search Tool for the Retrieval of Interacting Genes (STRING) database (http://string-db.org/) is designed to analyze PPI information. To evaluate potential PPI relationships, the previously identified DEGs were mapped to the STRING database. The PPI pairs with a combined score of 0.4 were extracted. Subsequently, the PPI network was visualized using the Cytoscape software (www.cytoscape.org/). Nodes with higher degree and higher betweenness centrality of connectivity tend to be more essential for maintaining the stability of the entire network. CytoHubba and CytoNCA are two plugins in Cytoscape that are used to calculate the degree and betweenness centrality of each protein node. In this study, genes with connectivity ≥10 and betweenness centrality ≥50 were identified as hub genes.

Diagnostic Values and Survival Analysis of Hub Genes
GraphPad Prism 8.0 software (GraphPad Software Inc., San Diego, CA, USA) was used to perform receiver operating characteristic (ROC) statistical analysis of the hub genes to evaluate their diagnostic value. The Kaplan-Meier plotter (http://kmplot.com/analysis/) mRNA lung cancer database was then used to evaluate the prognostic value of hub genes in patients with lung cancer. Patients with cancer were classified into two groups according to the median mRNA expression of each gene. $p < 0.05$ was deemed to indicate statistically significance.

**Single-sample Gene Set Enrichment Analysis (ssGSEA)**

The ssGSEA is an extension of the GSEA method used to calculate the enrichment score of each sample and gene set pairing. We conducted ssGSEA on the identified hub genes using the gene set variation analysis R package.

**Analysis of Hub Gene Expression in Tumors**

The University of Alabama at Birmingham CANcer data analysis portal (UALCAN) [18] is an interactive network resource (http://ualcan.path.uab.edu/). We analyzed the differential expression of hub genes in normal and tumor tissues, as well as their expression during tumor progression using relevant data from the UALCAN.

**Immunohistochemical Staining of Hub Genes**

The Human Protein Atlas (HPA) Database (https://www.proteinatlas.org/) provides detailed information on the distribution of proteins in human tissues and cells. We selected immunohistochemical images of the hub genes in lung cancer and normal tissues from the HPA database. These images were used to detect the differential expression of hub genes at the protein level.

**RESULTS**

**Identification of DEGs in Three GEO Datasets**
Table 1 shows the two datasets that were selected in this study. Based on the criteria ($p < 0.05$ and log fold change $> 2$), a total of 424 and 409 DEGs were identified from GSE116959 and GSE118370, respectively. The corresponding volcano maps for GSE116959 (Figure 1A) and GSE118370 (Figure 1B) are shown.

**Weighted Gene Co-Expression Network Analysis**

Using WGCNA, 10 modules were identified in GSE116959 (each color represents a module). Based on the Spearman correlation coefficient, a heat map of the module-trait relationship was generated to evaluate correlations between each module and the disease (Figure 2A, 2C). Four modules exhibited high correlations with LUAD; black ($r = -0.78$, $p = 6.2e-12$), disque4 ($r = 0.51$, $p = 1.1e-8$), saddle brown ($r = 0.62$, $p = 1.4e-8$), and dark magenta ($r = 0.28$, $p = 0.02$). Among them, disque4, saddle brown, and dark magenta were positively correlated with LUAD, including a total of 2,291 DEGs.

Eight modules were identified in GSE118370 (Figure 2B, 2D). Two modules were highly correlated with LUAD, Indian red 3 ($r = -0.91$, $p = 4.5e-5$) and dark sea green 2 ($r = 0.73$, $p = 7.1e-3$). Among them, dark sea green 2 was positively correlated with LUAD, containing 476 DEGs in total. A cross analysis was conducted on two datasets, resulting in identification of a total of 37 shared DEGs (Figure 2E).

**GO Enrichment Analysis of DEGs**

GO function enrichment analyses for DEGs were performed using the DAVID database. The enriched GO terms were divided into cellular component, molecular function, and biological process ontologies. The results indicated that, in the cellular component ontology, the DEGs were enriched in the extracellular region, extracellular region part, and extracellular space. In the molecular function ontology, the analysis showed that the DEGs were significantly enriched in metal ion binding, cation binding, and catalytic
activity. In the biological process ontology, the DEGs were enriched in cell differentiation, cellular developmental process, and regulation of response to stimulus (Figure 2F).

**PPI Network Construction and Hub Gene Identification**

We constructed a PPI network which involved a total of 35 nodes and 61 edges (Figure 3A). Afterwards, the degree and betweenness centrality of each protein node were calculated (Figure 3B, 3C). The analysis identified a total of five genes; cadherin 1 (CDH1), CD19, cellular retinoic acid binding protein 2 (CRABP2), matrix metalloproteinase 12 (MMP12), and DNA topoisomerase II alpha (TOP2A) (Table 2, Figure 4).

**Diagnostic Value and Survival Analysis of Hub Genes**

The diagnostic value of the hub genes was evaluated through ROC analysis of GSE116959 and GSE118370 (Figure 5A, 5B). The area under the ROC curve was > 75% for all five hub genes, indicating that these genes have strong diagnostic value. Subsequently, the prognostic value of the hub genes was evaluated using the Kaplan-Meier plotter bioinformatics analysis platform (Figure 5C-5G). The results showed that an increase in the expression levels of CDH1 was significantly negatively correlated with the prognosis of lung cancer. In contrast, an increase in the expression levels of CRABP2, MMP12, and TOP2A was significantly positively correlated with the prognosis of lung cancer. The results indicate that CRABP2, MMP12, and TOP2A are associated with a poor LUAD prognosis.

**ssGSEA and Analysis of Hub Gene Expression in Tumors**

By performing ssGSEA on the hub genes, we found that CRABP2 mainly affected glycerophospholipid metabolism and the calcium signaling pathway. MMP12 mainly affected the cell cycle and calcium signaling pathway. TOP2A mainly affected the cell cycle and protein export (Figure 6A-6C). Thereafter,
we analyzed the hub genes using the UALCAN. The results showed that the expression of CRABP2, MMP12, and TOP2A in LUAD tissue was significantly increased in tumor tissues compared with normal samples (Figure 6D–6F). We also found that the expression levels of CRABP2, MMP12, and TOP2A were significantly increased during the progression of tumors (Figure 6G–6I).

**Immunohistochemical Staining of Hub Genes**

The analysis of immunohistochemical images showed that the protein expression of CRABP2, MMP12, and TOP2A was significantly increased in LUAD compared with normal tissues (Figure 7).

**DISCUSSION**

In recent decades the incidence rate of LUAD has gradually increased, and it has become one of the most common types of lung cancer tumors. The prognosis of LUAD remains poor, and the 5-year relative survival rate is < 21% [19,20]. The treatment options for LUAD are currently limited to surgical resection and chemotherapy, both of which exhibit poor effectiveness [21,22]. The poor prognosis of LUAD is mainly attributed to the lack of specific biomarkers, which could permit early diagnosis and targeted treatment [23]. Therefore, the discovery of effective biomarkers has become a key factor in the treatment of LUAD. Bioinformatics is a new analytical method that differs from traditional experimental approaches. It is mainly used to process and analyze biological data via mathematical formulas and statistical methods [24]. Numerous studies have investigated biomarkers related to LUAD [25,26], but research conducted thus far has not identified effective biomarkers. It is therefore crucial to analyze LUAD from various aspects, identify the best target molecules for its treatment, and elucidate the biological pathways underlying its development and progression.

In the current study WGCNA revealed 37 shared DEGs in the two selected datasets. GO enrichment analysis indicated that the DEGs mainly pertained to
immune-related mechanisms, including extracellular regions, extracellular regions, extracellular space, metal ion binding, cation binding, catalytic activity, cell differentiation, cellular developmental processes, and regulation of responses to stimuli. These data further indicated the molecular mechanisms associated with LUAD, and suggested that tumor pathogenesis is a complex biological process caused by changes in the expression of specific genes and epigenetic alterations. The abnormal regulation of multiple genes can promote the occurrence and development of LUAD via different pathways.

To further search for hub genes, a PPI network was constructed and analysis of each protein node was performed. Five genes satisfied the criteria; CDH1, CD19, CRABP2, MMP12, and TOP2A. ROC analysis demonstrated that these five hub genes had high diagnostic value. The prognostic value of these five genes was then evaluated. Kaplan-Meier analysis indicated that increased expression of CRABP2, MMP12, and TOP2A can worsen LUAD, resulting in a poorer prognosis.

ssGSEA was conducted on the hub genes to investigate whether CRABP2, MMP12, and TOP2A affect LUAD. The results suggest that CRABP2 mainly affects glycerophospholipid metabolism and the calcium signaling pathway. MMP12 mainly affects the cell cycle and calcium signaling pathway. TOP2A mainly affects the cell cycle and protein export. Expression levels of CRABP2, MMP12, and TOP2A in LUAD were then investigated using the UALC. Compared with normal samples, CRABP2, MMP12, and TOP2A expression levels were significantly increased in LUAD tissue. Their expression was also significantly increased during tumor progression. These data indicate that CRABP2, MMP12, and TOP2A may lead to the occurrence and progression of LUAD, and have a sustained impact on LUAD. Lastly, immunohistochemical staining analysis revealed that protein expression of CRABP2, MMP12, and TOP2A in LUAD tissue was markedly higher than that in normal tissue. These findings further highlighted the importance of CRABP2, MMP12, and
TOP2A in LUAD.

In summary, CRABP2, MMP12, and TOP2A play a major role in the initiation and progression of LUAD. The present study indicates that increased CRABP2, MMP12, and TOP2A expression in LUAD can lead to tumor development. It was also shown that these genes are closely associated with a poorer prognosis. Therefore, CRABP2, MMP12, and TOP2A may be useful biomarkers of LUAD and become key targets for its treatment. Further investigation is required however, to clarify the mechanisms involved in LUAD and comprehensively examine the role of hub genes in this context.

CONCLUSION

Three hub genes related to LUAD were identified via bioinformatics analysis; CRABP2, MMP12, and TOP2A. Increased expression of these genes can lead to the occurrence of LUAD, and is the most unfavorable prognostic factor in patients with LUAD. Hence, CRABP2, MMP12, and TOP2A may be important biomarkers of LUAD. To date limited research has been conducted on the roles of CRABP2, MMP12, and TOP2A in LUAD. The results of the current study provide a powerful impetus for investigating the pathogenesis of LUAD and developing favorable therapeutic targets in the future.

ARTICLE HIGHLIGHTS

Research background

Adenocarcinoma of the lung (LUAD) is currently a cancer with high mortality. This study identified the biomarkers and therapeutic targets related to LUAD through bioinformatics analysis.

Research motivation

As of now, there are few biological analyses related to LUAD. Therefore, this study hopes to further study through Big data analysis.
Research objectives
To determine reliable prognostic biomarkers for early diagnosis and treatment of Adenocarcinoma of the lung.

Research methods
This article adopts bioinformatics methods such as GEO database, WGCNA, GEO2R, GO analysis, PPI network construction, UALCAN database, etc.

Research results
We found three genes, namely, cellular retinoic acid binding protein 2 (CRABP2), matrix Metalloprotein peptidase 12 (MMP12) and DNA Topoisomerase II α (TOP2A). The high expression of these genes is related to the poor prognosis of LUAD, and these Gene expression have high diagnostic value.

Research conclusions
We identified genes related to LUAD treatment and prognosis through bioinformatics methods, providing important information for the complete cure of LUAD.

Research perspectives
At present, there is little bioinformatics research related to LUAD. Through Big data screening, this study has more accurately identified the biomarkers and therapeutic targets related to LUAD, providing important information for the complete cure of LUAD in the future.

REFERENCES


Figure Legends

Figure 1. Volcano maps of differentially expressed genes in GSE116959 (A) and GSE118370 (B).

Figure 2. Weighted gene co-expression network analysis and gene ontology (GO) enrichment analysis of differentially expressed genes (DEGs). (A) Cluster dendrogram of co-expression genes in GSE116959. (B) Cluster dendrogram of co-expression genes in GSE118370. (C) Module-trait relationships in GSE116959. (D) Module-trait relationships in GSE118370. (E) Shared DEGs between GSE116959 and GSE118370. (F) Gene ontology enrichment analysis of the DEGs shared between the two datasets.

Figure 3. Protein–protein interaction (PPI) network construction and hub gene screening. (A) PPI network diagram of differentially expressed genes constructed based on the Search Tool for the Retrieval of Interacting Genes database. (B) Network diagram produced based on CytoHubba. (C) Network diagram created based on CytoNCA.

Figure 4. Shared hub genes based on analysis performed using CytoHubba and CytoNCA.
CDH1, cadherin 1; CRABP2, cellular retinoic acid binding protein 2; MMP12, matrix metallopeptidase 12; TOP2A, DNA topoisomerase II alpha

Figure 5. Receiver operating characteristic (ROC) analysis and Kaplan–Meier survival analysis. ROC analysis of hub genes in the (A) GSE116959
and (B) GSE118370 datasets. Kaplan–Meier survival analysis for (C) CD19, (D) CDH1, (E) CRABP2, (F) MMP12, and (G) TOP2A. AUC, area under the ROC curve; CDH1, cadherin 1; CRABP2, cellular retinoic acid binding protein 2; FPR, false positive rate; HR, hazard ratio; MMP12, matrix metallopeptidase 12; TOP2A, DNA topoisomerase II alpha; TPR, true positive rate

Figure 6. Single-sample gene set enrichment analysis (ssGSEA) and analysis of hub gene expression in tumors. (A–C) The ssGSEA of hub genes. (D–F) Expression of the hub genes in tumor tissues and normal samples. (G–I) Expression of the hub genes during tumor progression. LUAD, lung adenocarcinoma; TCGA, The Cancer Genome Atlas

Figure 7. Immunohistochemical staining of hub genes. CRABP2, cellular retinoic acid binding protein 2; MMP12, matrix metallopeptidase 12; TOP2A, DNA topoisomerase II alpha
Table 1. Data of the two microarray datasets derived from the Gene Expression Omnibus database

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Table 2. Data obtained using CytoHubba and CytoNCA

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ADAM8, ADAM metallopeptidase domain 8; CDH1, cadherin 1; CRABP2, cellular retinoic acid binding protein 2; CXCL14, C-X-C motif chemokine ligand 14; FCRL2, Fc receptor like 2; LTF, lactotransferrin; MMP12/13, matrix metallopeptidase 12/13; MYO6, myosin VI; SFRP4, secreted frizzled related protein 4; SRGAP1, SLIT-ROBO Rho GTPase activating protein 1; TOP2A, DNA topoisomerase II alpha
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