



Bioinformatics analysis of differentially expressed genes in tumor and paracancerous tissues of patients with lung adenocarcinoma

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Background: Lung adenocarcinoma is the main pathological type of non-small cell lung cancer (NSCLC). In this study, we analyzed the gene expression profile of lung adenocarcinoma tumor and paracancerous tissues by bioinformatics to assess the genes and signal pathways related to lung adenocarcinoma.

Methods: The expression data of GSE7670, GSE27262, and GSE32863 were downloaded from the Gene Expression Omnibus (GEO) database. The three microarray data sets were integrated to obtain common differential expression genes of lung adenocarcinoma tumor and adjacent tissues. The STRING database was used to construct the protein-protein interaction (PPI) network of lung adenocarcinoma and mine the gene modules and core genes in the network, and the online tools, GEPIA and Kaplan-Meier plotter were used to further verify and analyze the core genes.

Results: There were 109 pairs of lung adenocarcinoma tissues and matched paracancerous normal lung tissues in the three data sets. Eighty-three differentially expressed genes were identified, including 16 up-regulated and 67 down-regulated genes, and 60 differentially expressed genes were successfully incorporated into the PPI network complex. Eleven core genes were identified in the PPI network complex, including three up-regulated (*COMP*, *SPP1*, *COL1A1*) and eight down-regulated genes (*CDH5*, *CAV1*, *CLDN5*, *LYVE1*, *IL6*, *VWF*, *TEK*, *PECAM1*). These core genes were verified by the GEPIA tumor database. Survival analysis showed that expression of the core genes was significantly related to the prognosis of lung adenocarcinoma. KEGG pathway analysis of core genes showed six genes (*COMP*, *SPP1*, *COL1A1*, *IL6*, *VWF*, *TEK*) were significantly enriched in the PI3K-Akt signaling-pathway ($P=1.62E-06$).

Conclusions: By analyzing the differential expression genes of lung adenocarcinoma and paracancerous normal tissues with bioinformatics, 11 genes with significant differential expression and significant influence on prognosis were identified. The findings may provide new concepts for developing diagnosis and treatment targets and prognosis markers for lung adenocarcinoma.

Keywords: Lung adenocarcinoma; bioinformatics analysis; differential expression genes; PI3K-Akt signaling-pathway; Gene Expression Omnibus (GEO) database

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Introduction

Lung cancer is the most common and deadly malignant tumor in humans with an incidence and mortality rate of 11.6% and 18.4% respectively (1). Non-small cell lung cancers (NSCLC) are the most common type of lung cancer, of which lung adenocarcinoma is the main pathologic type, accounting for 40% of lung cancer (2). Most lung adenocarcinoma is identified in the late stage, and the 5-year survival rate is low (3), possibly because there is currently no specific biomarker to facilitate early diagnosis and prognosis prediction (3). A reliable prognostic biomarker would help assess prognosis, evaluate therapeutic effects, and clarify the mechanism of lung cancer. The gene chip is a systematic high-throughput method for detecting and analyzing differentially expressed genes in different tissues, which can help to find prognostic genes or biomarkers for cancers. With the rapid development and application of gene chip technology, a large amount of gene data have been accumulated and the best methods how to mine genes from gene data has become a hot research topic (4). In this study, we screened the core genes of lung adenocarcinoma by the bioinformatic analysis of gene chip data of tumor tissue and matched paracancerous tissue from the gene chip public database Gene Expression Omnibus (GEO). These core genes can be used to determine disease diagnosis, prognosis judgment, and the mechanism research of lung adenocarcinoma in the future. We present the following article in accordance with the MDAR reporting checklist (available at <http://dx.doi.org/10.21037/jtd-20-3453>).

Methods

Microarray data information

The GEO database (<https://www.ncbi.nlm.nih.gov/>) is a free and open public database. The data of three gene expression profiles (GSE7670, GSE27262, GSE32863) were downloaded from the database and included 26, 25, and 58 pairs of lung adenocarcinoma and matched paracancerous normal lung tissue samples, respectively. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Screening of differentially expressed genes (DEGs)

Data of the three profiles were analyzed using an online analysis program based on the R language, GEO2R. Venn software was used to analyze the differential genes of the profiles, and commonly up- and down-regulated differential

genes were obtained.

Gene ontology analysis (GO) and Kyoto Encyclopedia of gene and genome (KEGG) pathways analysis

The common DEGs selected from the above three groups were uploaded to the online analysis platform DAVID (<https://david.ncifcrf.gov/>) for GO and KEGG pathway analysis. The encoded proteins of DEGs were analyzed by molecular function (MF), cellular component (CC), and biological process (BP) to study their GO functional and pathway enrichment. Differences with $P < 0.05$ were considered statistically significant.

Protein-protein interaction (PPI) network and core gene screening

A PPI network was constructed by analyzing the PPI relationship between DEGs using the STRING database, and the threshold condition was a confidence score ≥ 0.4 (5). The results of analyzed data were then imported into Cytoscape for visualization analysis, and node connectivity was calculated with the plug-in MCODE to screen for the central node of the network. Genes corresponding to the central node were considered core genes.

Validation and survival analysis of core genes

GEPIA (<http://gepia.cancer-pku.cn/>) is an online website tool based on the TCGA and GTEX databases (6) and was used to further verify the core genes. The Kaplan-Meier plotter is an online deposit of the survival analysis data of EGA, TCGA, and GEO (Affymetrix microarrays only) databases. In this study, the Kaplan-Meier plotter was used to perform survival analysis for the core genes.

Statistical analysis

Differentially expressed genes with an adjusted P value < 0.05 and $|\log_{2}FC| > 2$ were considered statistically significant by using *t*-test. The Kaplan-Meier plotter was used to perform survival analysis for the core genes. Differences with $P < 0.05$ were considered statistically significant.

Results

Identification of DEGs in lung adenocarcinoma

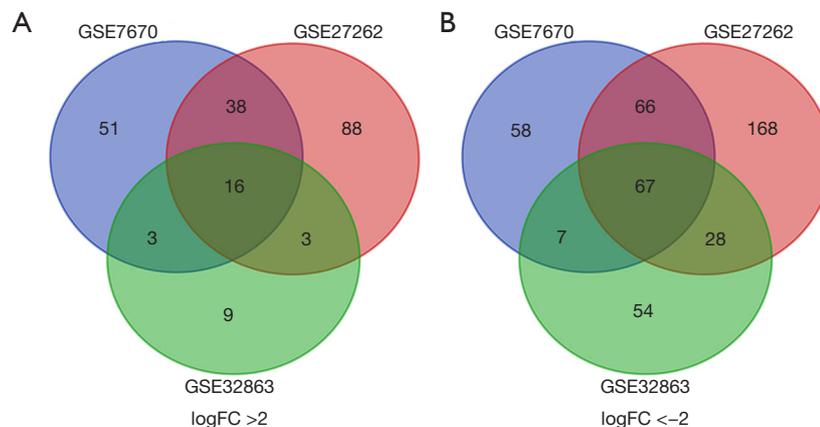


Figure 1 Eighty-three common differentially expressed genes identified by Venn software. (A) Sixteen co-up-regulated genes ($\log_{2}FC > 2$) and (B) 67 co-down-regulated genes ($\log_{2}FC < -2$).

Table 1 Eighty-three common differentially expressed genes

DEGs	Gene symbol
Up-regulated	<i>CEACAM5, CDH3, SPINK1, SFN, CDC20, HMGB3, TOP2A, COMP, CRABP2, GCNT3, ETV4, CST1, SPP1, COL1A1, MMP11, EEF1A2</i>
Down-regulated	<i>FMO2, ABCA8, SOCS2, SFTPC, MFAP4, SVEP1, IL33, PECAM1, TCF21, TGFBR3, PGC, ADH1B, LPL, CLDN5, FABP4, SOSTDC1, EDNRB, SCGB1A1, GPC3, FCN3, HIGD1B, CA4, TEK, SFTPD, STX11, FAM107A, ADAMTS1, GPX3, ANOS1, ACKR1, AGER, FOSB, CAV2, RGCC, VWF, MARCO, LYVE1, HBEGF, WIF1, LAMP3, EPAS1, RAMP3, CLIC5, SPOCK2, CD36, LDB2, MME, TSPAN7, CAV1, CLDN18, AQP4, CDH5, MT1M, TNNC1, CFD, IL6, CYP4B1, SMAD6, ADIRF, HBB, ITM2A, FHL1, HYAL1, TMEM100, CPB2, DUOX1, KLF4</i>

The three data sets consisted of 109 pairs of lung adenocarcinoma and matched paracancerous normal lung tissues. The GEO2R analysis showed 108 up-regulated genes and 198 down-regulated genes in GSE7670, 145 up-regulated genes and 329 down-regulated genes in GSE27262, and 31 up-regulated genes and 156 down-regulated genes in GSE32863. A Venn diagram was created according to the different gene expression patterns of the three data sets, and 83 common differentially expressed genes were finally obtained (Figure 1). Compared with paracancerous tissues, there were 16 up-regulated genes ($\log_{2}FC > 2$) and 67 down-regulated genes ($\log_{2}FC < -2$) in lung adenocarcinoma tissues (Table 1 and Figure 1).

GO and KEGG pathway analysis

The GO enrichment analysis of 83 differentially expressed genes on the DAVID website showed differentially expressed genes mainly participated in the following processes: position regulation of transcription from

RNA polymer II promoter, cell adhesion, angiogenesis, and position regulation of gene expression of the BP; extracellular exosome, plasma membrane, extracellular space, and extracellular region of the CC; calcium ion binding, heparin binding, protein kinase binding, and cytokine activity of MF (Table 2).

KEGG analysis showed that the differentially expressed genes were mainly enriched in six signaling pathways, including the PI3K-Akt signaling pathway, malaria, focal adhesion, ECM-receptor interaction, cell adhesion molecules (CAMs), and leukocyte transendothelial migration (Table 3).

Construction of PPI network and screening of core genes

Eighty-three differentially expressed genes were imported into the STRING database to construct the PPI network, and 60 differentially expressed genes were incorporated into the PPI network complex (Figure 2A). Cytotype MCODE software further identified 11 core genes (Figure 2B) in the PPI network complex, three of which were up-regulated (*COMP, SPP1,*

Table 2 GO enrichment analysis of differentially expressed genes

Category	Term	Count	%	P value	FDR
GOTERM_BP_DIRECT	GO:0045944~positive regulation of transcription from RNA polymerase II promoter	9	7.5	0.011191	15.38657
GOTERM_BP_DIRECT	GO:0007155~cell adhesion	7	5.9	3.00E-04	0.44389
GOTERM_BP_DIRECT	GO:0001525~angiogenesis	5	4.2	0.005482	7.83715
GOTERM_BP_DIRECT	GO:0010628~positive regulation of gene expression	4	3.3	0.03919	44.76037
GOTERM_CC_DIRECT	GO:0070062~extracellular exosome	20	16.7	0.00632	6.878697
GOTERM_CC_DIRECT	GO:0005886~plasma membrane	18	15.0	0.040614	37.25272
GOTERM_CC_DIRECT	GO:0005615~extracellular space	15	12.5	1.65E-04	0.18545
GOTERM_CC_DIRECT	GO:0005576~extracellular region	7	5.9	0.035697	33.54157
GOTERM_MF_DIRECT	GO:0005509~calcium ion binding	8	6.7	0.022598	23.71515
GOTERM_MF_DIRECT	GO:0008201~heparin binding	5	4.2	0.00188	2.203801
GOTERM_MF_DIRECT	GO:0019901~protein kinase binding	4	3.3	0.007307	8.318523
GOTERM_MF_DIRECT	GO:0005125~cytokine activity	4	3.3	0.025677	26.51256

Table 3 KEGG pathway enrichment analysis of differentially expressed genes

Pathway ID	Name	Count	%	P value	Genes
hsa04151	PI3K-Akt signaling pathway	7	5.9	0.021716	<i>VWF, IL6, COMP, TEK, COL1A1, SPP1</i>
hsa05144	Malaria	6	5.0	1.92E-05	<i>IL6, CD36, COMP, PECAM1, ACKR1, HBB</i>
hsa04510	Focal adhesion	6	5.0	0.009898	<i>VWF, CAV2, CAV1, COMP, COL1A1, SPP1</i>
hsa04512	ECM-receptor interaction	5	4.2	0.002175	<i>VWF, CD36, COMP, COL1A1, SPP1</i>
hsa04514	Cell adhesion molecules (CAMs)	5	4.2	0.016157	<i>CLDN18, CLDN5, PECAM1, CDH3, CDH5</i>
hsa04670	Leukocyte transendothelial migration	4	3.3	0.037066	<i>CLDN18, CLDN5, PECAM1, CDH5</i>

COL1A1) and eight of which were down-regulated (*CDH5, CAV1, CLDN5, LYVE1, IL6, VWF, TEK, PECAM1*).

Validation of core genes with GEPIA tumor database

Query of the GEPIA tumor database identified that *COMP, SPP1*, and *COL1A1* were significantly higher in lung adenocarcinoma than in normal lung tissues (Figure 3A,B,C), while *CDH5, CAV1, CLDN5, LYVE1, IL6, VWF, TEK*, and *PECAM1* were significantly lower in lung adenocarcinoma (Figure 3D,E,F,G,H,I,J,K). These results were consistent with the previous GEO2R analysis.

Relationship between core genes and patient prognosis

Survival analysis performed using the Kaplan-Meier plotter

showed that the expression of 11 core genes (*COMP, SPP1, COL1A1, CDH5, CAV1, CLDN5, LYVE1, IL6, VWF, TEK, PECAM1*) was related to lung adenocarcinoma prognosis ($P < 0.05$) (Figure 4A,B,C,D,E,F,G,H,I,J,K). Patients with a high expression of *SPP1, COL1A1, LYVE1*, and *IL6*, or, a low expression of *COMP, CDH5, CAV1, CLDN5, VWF, TEK*, and *PECAM1*, had a worse prognosis (Figure 4A,B,C,D,E,F,G,H,I,J,K).

KEGG pathway analysis of core genes

The KEGG pathway enrichment of 11 core genes was reanalyzed using DAVID software. This showed that six genes (*COMP, SPP1, COL1A1, IL6, VWF, TEK*) were significantly enriched in the PI3K-Akt signaling pathway ($P = 1.62E-06$, Table 4 and Figure 5).

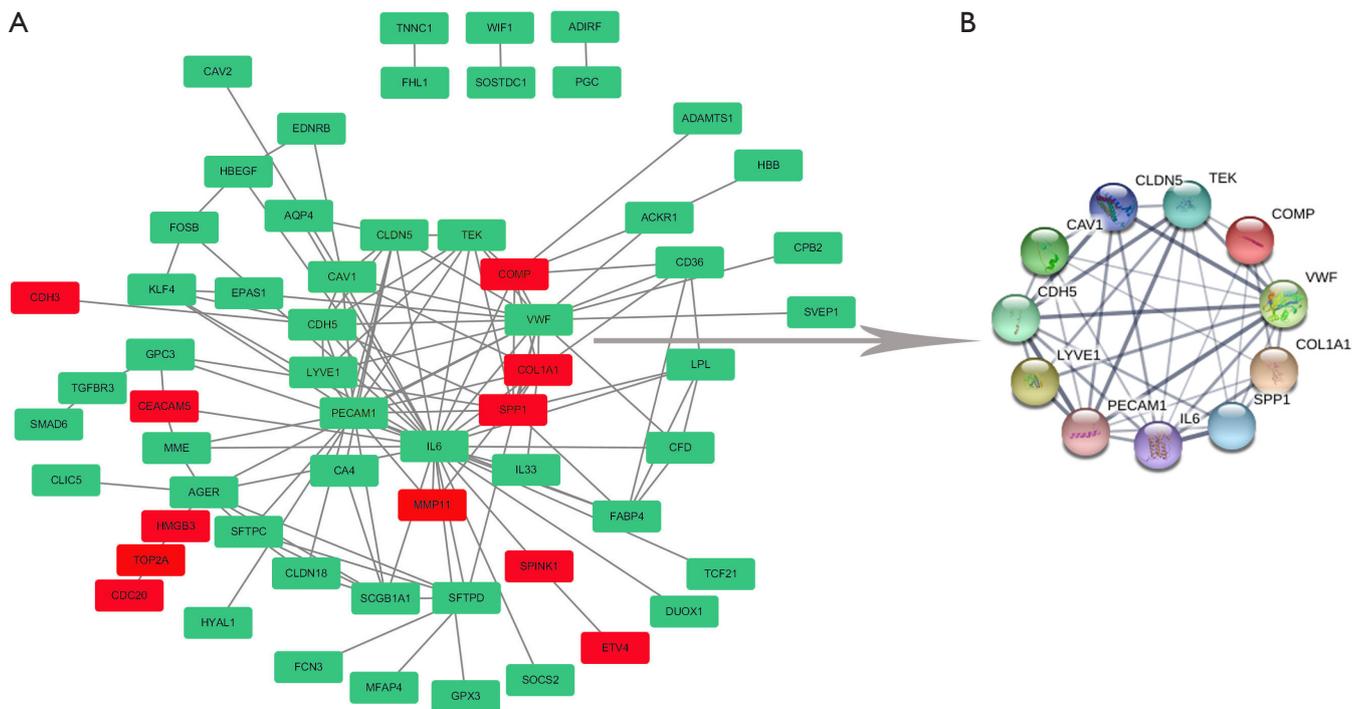


Figure 2 Protein-protein interaction (PPI) network diagram and core genes. (A) PPI network diagram constructed from the STRING database. Red nodes indicate up-regulated differentially expressed genes, and green nodes indicate down-regulated differentially expressed genes; (B) 11 core genes identified by Cytotype MCODE software.

Discussion

In this study, three gene expression profiles (GSE7670, GSE27262, GSE32863) containing 109 pairs of lung adenocarcinoma and matched paracancerous normal lung tissues were analyzed. This revealed 83 common differential expression genes including 16 up-regulated and 67 down-regulated genes. The GO analysis showed that the differentially expressed genes were mainly involved in position regulation of transcription from RNA polymer II promoter, extracellular exosome, calcium ion binding, etc. KEGG analysis showed that differentially expressed genes were mainly enriched in the PI3K-Akt signaling pathway, malaria, etc. These data indicate that tumor pathogenesis is a complex biologic process driven by specific genes and epigenetic changes. Abnormal regulation of multiple genes can promote the occurrence and development of lung adenocarcinoma through different mechanisms.

To further screen core genes, a PPI network was constructed using the STRING database, visualized by Cytotype, and screened by MCODE plug-in. Finally, 11 core genes were identified, including three up-regulated

genes (*COMP*, *SPP1*, and *COL1A1*) and eight down-regulated genes (*CDH5*, *CAV1*, *CLDN5*, *LYVE1*, *IL6*, *VWF*, *TEK*, and *PECAM1*). Among these, *SPP1*, *CDH5*, and *VWF* have been reported in other literature (7). These core genes were verified by the GEPIA tumor database. Survival analysis results obtained using the Kaplan-Meier plotter online website tool showed that expression of the 11 core genes was significantly related to lung adenocarcinoma prognosis: patients with a high expression of *SPP1*, *COL1A1*, *LYVE1*, and *IL6*, or a low expression of *COMP*, *CDH5*, *CAV1*, *CLDN5*, *VWF*, *TEK*, and *PECAM1* had a worse prognosis. Many cancers have specific diagnostic and prognostic markers. For example, alpha-fetoprotein (AFP) is a marker for liver cancer (8), while prostate-specific antigen (PSA) is a marker for prostate cancer (9). However, lung cancer lacks specific diagnostic and prognostic markers. Among 11 core genes, three were up-regulated (*COMP*, *SPP1*, *COL1A1*) and survival analysis showed that patients with a high expression of *SPP1* and *COL1A1* had a worse prognosis. Previous studies reported that the GRGDS sequence of *SPP1* is related to cell adhesion and promotes tumor cell metastasis and invasion (10), which may explain

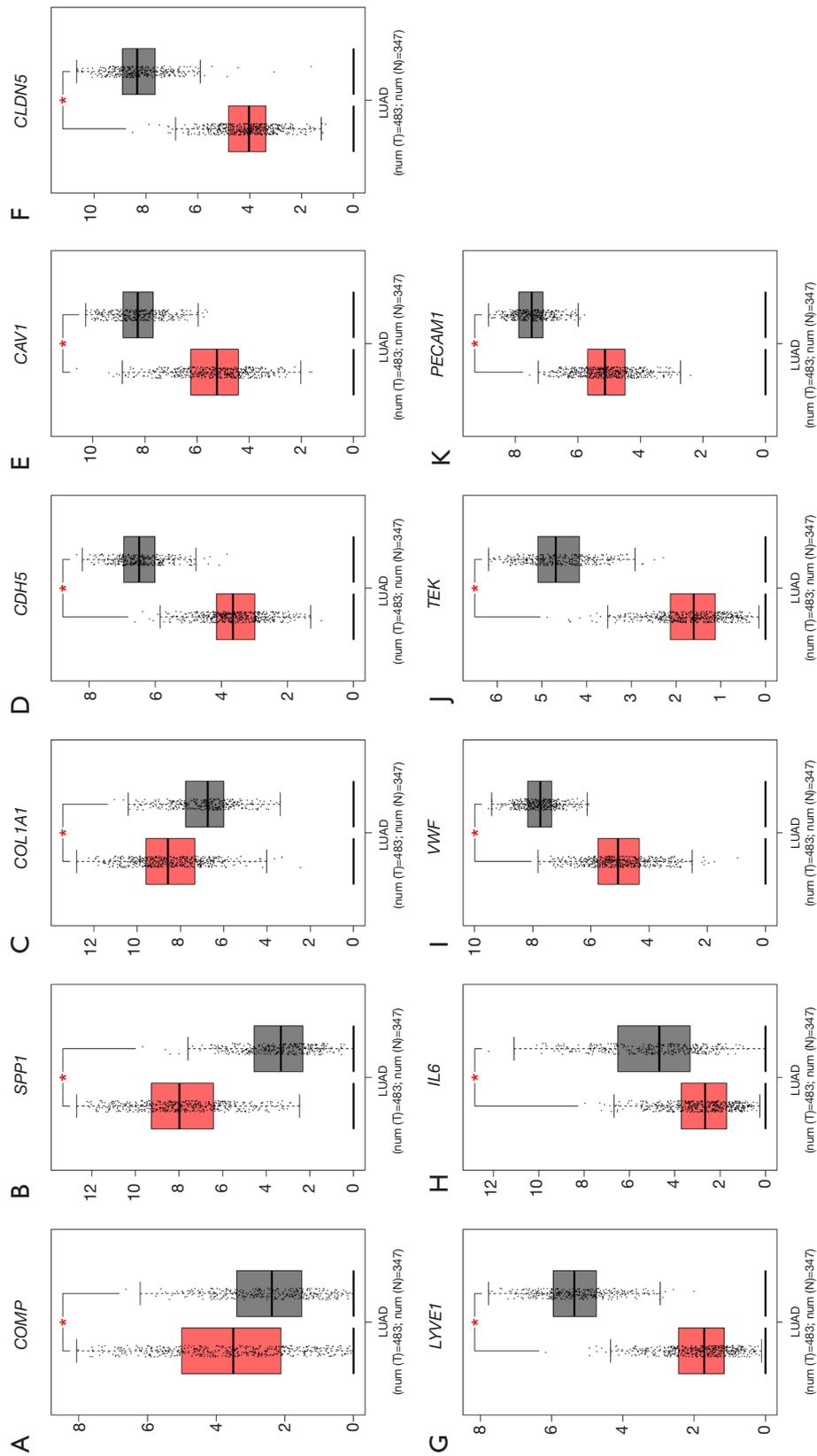


Figure 3 Verification of 11 core genes using the GEPIA tumor database. (A) *COMP*, (B) *SPP1*, (C) *COL1A1*, (D) *CDH5*, (E) *CAV1*, (F) *CLDN5*, (G) *LYVE1*, (H) *IL6*, (I) *VWF*, (J) *TEK*, (K) *PECAM1*. LUAD, lung adenocarcinoma; T, tumor tissues (red); N, normal tissues (gray). *P<0.05.

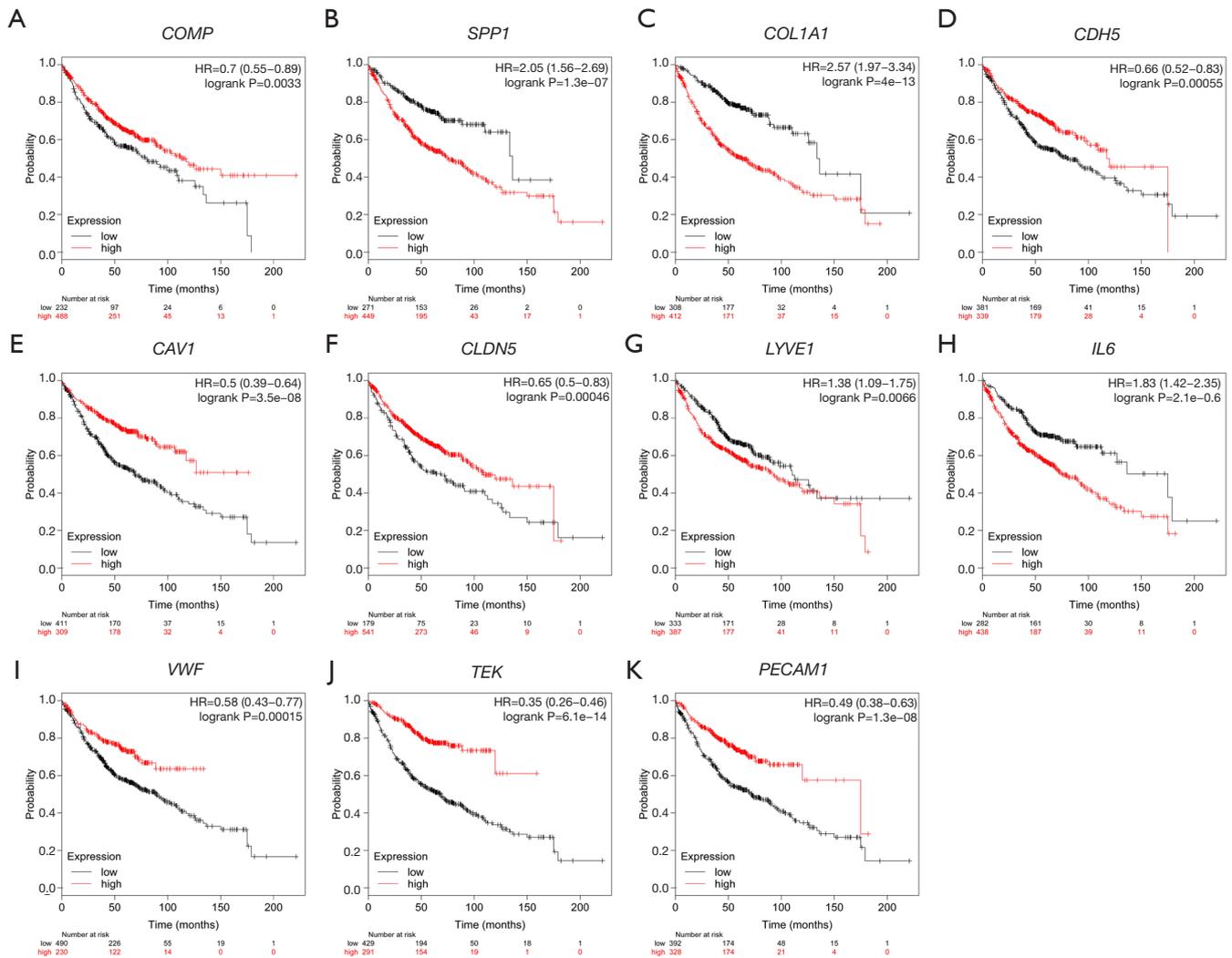
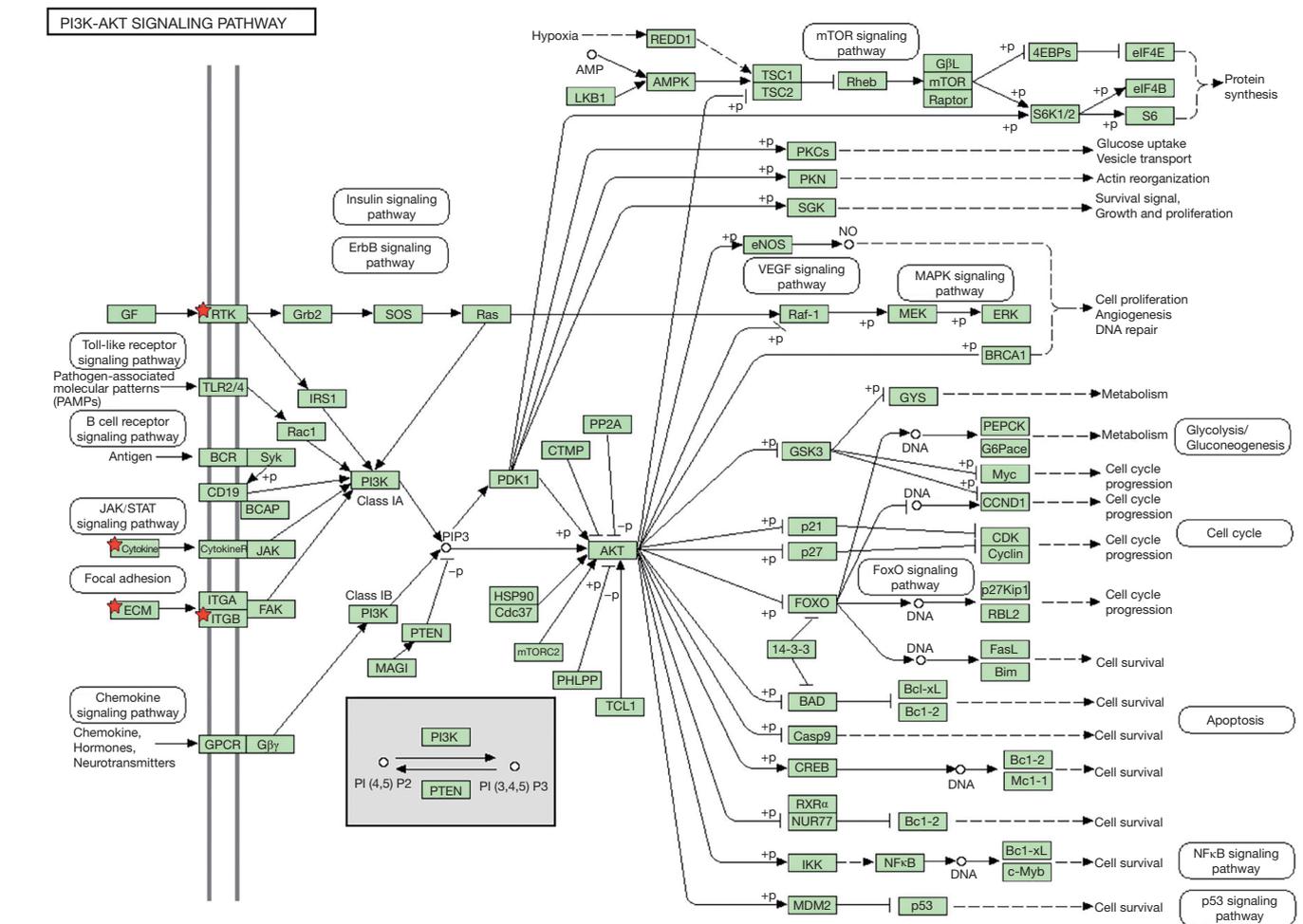


Figure 4 Survival curve of core gene expression and prognosis in lung adenocarcinoma. (A) *COMP*, (B) *SPP1*, (C) *COL1A1*, (D) *CDH5*, (E) *CAV1*, (F) *CLDN5*, (G) *LYVE1*, (H) *IL6*, (I) *VWF*, (J) *TEK*, (K) *PECAM1*. The red curve represents the high expression group, and black curve the low expression group.

Table 4 KEGG pathway enrichment analysis of 11 core genes

Pathway ID	Name	Count	%	P value	Genes
hsa04151	PI3K-Akt signaling pathway	7	37.9	1.62E-06	<i>VWF, IL6, COMP, TEK, COL1A1, SPP1</i>
hsa04510	Focal adhesion	5	27.1	1.03E-04	<i>VWF, CAV1, COMP, COL1A1, SPP1</i>
hsa04512	ECM-receptor interaction	4	21.7	1.67E-04	<i>VWF, COMP, COL1A1, SPP1</i>
hsa05144	Malaria	3	16.3	0.002099	<i>IL6, COMP, PECAM1</i>
hsa04620	Toll-like receptor signaling pathway	3	16.3	0.008016	<i>IL6, SPP1</i>
hsa04670	Leukocyte transendothelial migration	3	16.3	0.009717	<i>CLDN5, PECAM1, CDH5</i>
hsa04514	Cell adhesion molecules (CAMs)	3	16.3	0.016707	<i>CLDN5, PECAM1, CDH5</i>



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(c) Kanehisa Laboratories

List genes are shown in red

Figure 5 Six core genes (*COMP*, *SPP1*, *COL1A1*, *IL6*, *VWF*, *TEK*) were significantly enriched in the PI3K-Akt signaling pathway. RTK indicates *TEK*; Cytokine indicates *IL6*; ECM indicates *SPP1* and *VWF*; ITGB indicates *COMP* and *COL1A1*.

why the prognosis of patients with high expressions of *SPP1* is worse. *COL1A1* is an important strand of the type I collagen triple helix, which is closely related to tumors and acts as a carcinogenic gene to promote tumor cell growth (11-13). Mori *et al.* found that *COL1A1* plays an important role in differentiation and metastasis of human bladder cancer (14). Liu *et al.* confirmed that *COL1A1* mediates breast cancer metastasis and is a potential therapeutic target for breast cancer (15). In addition, *COL1A1* is an important marker of hepatocarcinogenesis and development (16). However, there are few studies concerning the role of *COL1A1* in lung cancer. Further study on the role of *SPP1* and *COL1A1* is needed to confirm them as specific biomarkers for the diagnosis and prognosis judgment of

lung adenocarcinoma.

The PI3K-Akt signaling pathway is an important signal pathway in the human body. This signaling pathway controls cellular BP of tumor development through a phosphorylation cascade of downstream proteins that affect cell proliferation, apoptosis, cell cycle regulation, and angiogenesis. Imbalance of the PI3K-Akt pathway plays an important role in the development of NSCLC as the PI3K-Akt pathway is activated in about 90% of NSCLC cell lines (17). Mutation of *EGFR*, *PTEN* deletion or mutation, and *PI3K* mutation or amplification can all activate the PI3K-Akt pathway, promote NSCLC tumor cell proliferation and migration, and lead to tumor progression (18). In this study, we re-analyzed the enrichment of the KEGG

pathway of 11 core genes using DAVID software to show that six genes (*COMP*, *SPP1*, *COL1A1*, *IL6*, *VWF*, *TEK*) were significantly enriched in the PI3K Akt-signaling pathway. The results demonstrate that the occurrence and development of lung adenocarcinoma is closely related to the PI3K-Akt signaling pathway. Further study of the role of PI3K-Akt signaling in lung adenocarcinoma will provide new directions for understanding its mechanisms and promote the development of therapeutic targets.

With rapid developments in high-throughput technology, many experimental data related to lung adenocarcinoma have been obtained. In this study, existing public database and analysis tools were used to integrate multiple groups of lung adenocarcinoma data and conduct unified processing. We identified specific genes and pathways related to the prognosis of lung adenocarcinoma, which will be helpful for the diagnosis, treatment, prognosis judgement, and in-depth study of the mechanisms of this deadly disease in the future. The results also provide valuable information for future research and the development of new drugs. Nonetheless, this study has some limitations. Firstly, the experimental verification of core genes is lacking, and we plan to carry this out immediately. Secondly, the sample size was small and only included three data sets. Our own clinical data should be further supplemented to verify the findings in this study. Finally, only 720 lung adenocarcinoma samples were included in the survival analysis. Further experiments are needed to examine the specific molecular mechanisms of lung adenocarcinoma.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/jtd-20-3453>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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