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Comparison of gene expression profiles in healthy individuals and people with lung cancer using the meta-analysis method

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ABSTRACT

Advances in the early detection of cancer are a way for treatment to be effective. However, due to the inability of early diagnose and treatment for lung cancer, the death rate of this type of cancer is high. Usually, a high percentage of patients are diagnosed at a stage where they are not able to receive treatment. The purpose of this study was the comparison of gene expression profiles in healthy individuals and people with lung cancer. The raw data sets GSE10072 and GSE19804 were taken from the GEO online database. Differentially expressed genes (DEGs) were identified between the non-tumor and tumor tissue samples using a meta-analysis investigation. Then, gene ontology and biological pathway analysis were performed with the Enrichr online server. The protein-protein interaction network of genes obtained from the meta-analysis investigation was drawn and analyzed using the String Online database and Cytoscape Software. Meta-analysis results showed a total of 515 differentially expressed genes. The results of the functional processes and biological pathway revealed that differentially expressed genes were mainly enriched in positive regulation of cell differentiation, regulation of cell population proliferation, regulation of epithelial cell differentiation, positive regulation of epithelial cell proliferation, response to growth factor, defense response to the tumor cell, cellular response to UV, regulation of cell cycle process, cell adhesion molecules, PPAR signaling pathway, TNF signaling pathway, ECM-receptor interaction, p53 signaling pathway, PI3K-Akt signaling pathway, and Cell cycle. Finally, key genes related to lung cancer, including IL6, MMP9, VWF, PECAM1, FOS, and CAV1 were identified. In conclusion, comparisons of gene expression profiles in healthy individuals and people with lung cancer identified some key genes that can act as lung cancer markers and can be used to predict new findings on cancer. These genes can play an important role in diagnosis and early cancer treatment.

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Introduction

The lung, an important organ that is often damaged by tumors, pathogens, and other environmental particles, contains a large number of innate immune cells (1). Lungs contain mucus and are constantly exposed to environmental and autologous stimuli, and are a place with a high occurrence of primary and metastatic tumors (2). Therefore, to maintain pulmonary homeostasis, a rapid and effective immune response is required to prevent tumorigenesis and pathogen invasion (3). The lung of a healthy human contains a unique and active bacterial community, which is characterized by the movement of non-sterile air in two directions and mucus in the inlet and outlet of the airways (4). Lung disease is caused by a change in the lung environment.

Cancer is a genetic disease and non-communicable that occurs due to a change in the division and death program of cells (5,6). Cancer is a disease in which cells grow out of control. The main cause of cancer-related deaths worldwide is lung cancer, which accounts for 18.4% of death (7). Lung cancer is one of the most important cancers in human societies, which is very important due to its high prevalence and social and economic effects. Lung cancer is common in industrialized countries (due to the presence of contaminants) (8,9). According to the origin of the cell that has undergone transformation and cancer, there are different types of lung cancer including small-cell lung cancer (SCLC(, and non-small-cell lung cancer (NSCLC((10), which are characterized by mutations and phenotypic appearance and often show varying degrees of heterogeneity, aggressiveness, and response/resistance to treatment (11). The disease is initially asymptomatic and is usually diagnosed in advanced stages (12). Non-small cell lung cancer (NSCLC) is the most common type of lung cancer and is usually treated with surgery or chemotherapy in the early stages (13). Lung cancer occurs with the gradual increase of genetic and epigenetic changes (14,15). The main cause of lung cancer is tobacco smoke (16).

A powerful method that combines data from related but separate studies to obtain results with higher statistical power and precision is a meta-analysis (17,18). Considering that lung cancer treatment methods currently do not cure most lung cancer patients and invasive diagnostic

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methods (for example, through biopsy and bronchoscopy) often cause pain to patients, meta-analysis can help in finding biomarkers for early detection of this type of cancer. meta-analysis is not only a statistical method but also an advanced and almost complete description of the entire data (19). It increases statistical precision and accuracy and results in the production of a highly accurate assessment of the expression of differentially expressed genes (19). Identifying and understanding the characteristics that contribute to the growth of cancer is achieved by analyzing the gene expression profiles and classifying the type of cancer. The analysis of microarray of cancer data will help to create better insights about cancer, plan for taking decisive action, and improve the cancer diagnosis method (20). In this study, we compare gene expression profiles in healthy individuals and people with lung cancer.

Materials and Methods

Preparation of raw data of microarray

There is a valuable resource of publicly available gene expression data that can be integrated and analyzed to derive new hypotheses and knowledge. One of these sources is the Gene Expression Omnibus database (GEO). The Gene Expression Omnibus is deposited at the National Center for Biotechnology Information (NCBI) database and makes available high-throughput data from the scientific community (21). Two gene expression profiles, GSE10072 and GSE19804, including non-tumor and tumor tissue samples, were downloaded from the GEO database. In the dataset of GSE10072, gene expression was investigated using Affymetrix HG-U133A arrays on 135 fresh-frozen adenocarcinoma and paired uninvolved lung tissue samples from current, former, and never smokers. Normalization was performed on the remaining 135 microarrays. After normalizing, 13 samples were left out because there is a low percentage of tumor cells in the tumor tissues. This study included 122 samples, of which 15 replicates were identified, resulting in 107 expression values from 58 tumor, 49 non-tumor tissues, 20 never-smokers, 26 former smokers, and 28 current smokers. In dataset, GSE19804, [HG-U133_Plus_2] Affymetrix array was used and RNA was extracted from paired tumor and normal tissues for gene expression analysis in general. This dataset included 120 samples.

Pre-processing of microarray data

Data preprocessing is the first important step in microarray data analysis. Depending on the biological characteristics of the data, the best method should be used among different methods (22). Using the Limma package in the R software, the quality was checked using the principle component analysis method (PCA) and then normalization was done. principle component analysis is an important and common method in dimension reduction, visualization, and identifying the main variable in total data (22,23).

Meta-analysis of gene expression profiles

Meta-analysis was performed using sva (24) and limma (25) packages of R statistical software (http://www.r-project.org/). Two datasets from two different platforms were normalized and integrated. We used the ComBat method (26) implemented in the sva package to batch-adjust the gene expression data of the merged dataset. The ComBat method merges the information from several genes with similar expression distributions in each dataset to estimate the average and variance in each of those genes (27). Differentially expressed genes were identified between non-tumor and tumor tissue samples based on |Fold Change| > 1 and p-Value < 0.05.

Gene ontology and biological pathway analysis of differentially expressed genes

Enrichr) http://amp.pharm.mssm.edu/Enrichr(is an online server that provides enrichment analysis using a list of genes (28). Enrichr includes large and varied gene libraries for analysis and loading. Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) were analyzed using the Enrichr database. The GO project describes gene products in every living organism (29). KEGG provides a repository of genomic, chemical, and systemic activity data (30). The criteria for identifying functional processes and biological pathways were based on p-Value < 0.05.

Protein-protein interaction network of differentially expressed genes

The protein-protein interaction network was drawn using the String web tool) version 11.5(, and then the network was entered into Cytoscape software (version 3.9.1) for visualization and analysis. The String software enables physical and functional correlation by evaluating and establishing protein-protein interactions (31). The interaction score of 0.15 in String software was considered. Cytoscape is software for interacting biomolecular networks using expression data (32). Hub genes using the CytoNCA plugin were identified based on degree centrality, betweenness centrality, and closeness centrality.

Results

Microarray data used and normalization before of meta-analysis

We downloaded the datasets with accession numbers GSE10072 and GSE19804 from the GEO database. Samples from 58 tumors and 49 non-tumor tissues in the GSE10072 database and 60 tumors and 60 non-tumor tissues in the GSE19804 database were used for meta-analysis in this study, which is shown in Table 1. Data normalization is an important issue in research work, whether targeted or untargeted. Without normalization of microarray data, the data can become erroneous and suboptimal, which leads to misleading and confusing results. The box plot of the data before and after normalization, as well as

Table 1. A summary of the characteristics of the raw data used in the meta-analysis.

GEO accession no.	Samples	Platform
GSE10072	58 tumor and 49 non-tumor tissues	[HG-U133A] Affymetrix
GSE19804	60 tumor and 60 non-tumor tissues	[HG-U133_Plus_2]Affymetrix

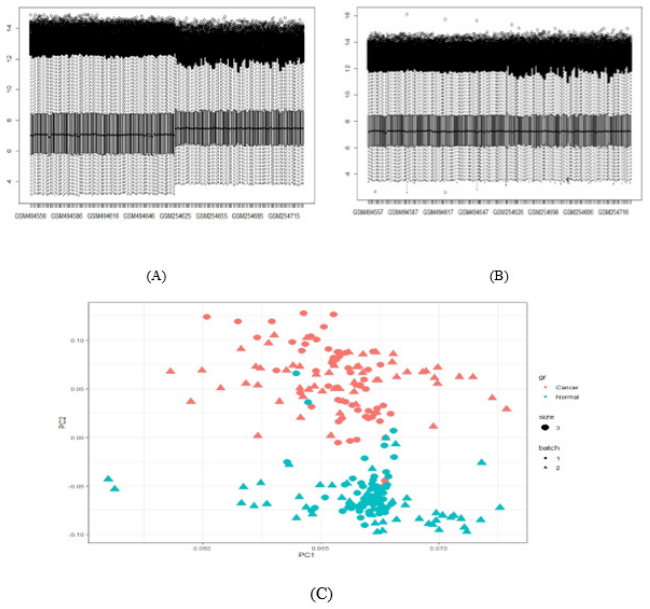

Figure 1. Microarray data before (A), after normalization (B), and PCA diagram after normalization (C).

the PCA diagram after normalization, was drawn is shown in Figure 1.

Identification of differentially expressed genes using meta-analysis

Meta-analysis is the analysis of related but independent data for a quantitative assessment of the studied phenomenon (33). The DEGs between the non-tumor and tumor tissue samples were identified using the meta-analysis. The screening thresholds for differentially expressed genes were set at |Fold Change| > 1 and p-Value < 0.05. Based on the aforementioned screening thresholds, among the 515 differentially expressed genes, 167 up- and 348 down-regulated were identified.

Gene ontology and biological pathway analysis of differentially expressed genes

After finding differentially expressed genes using the meta-analysis, these genes were used for the input of the Enrichr online server. The functional processes using the genes obtained from the meta-analysis showed, there were a total of 685 functional processes with p-Value ≤ 0.05. In our research, functional processes related to lung cancer are listed in Table 2 the important processes in lung cancer are positive regulation of cell differentiation, regulation of cell population proliferation, regulation of epithelial cell differentiation, positive regulation of epithelial cell proliferation, response to growth factor, defense response to the tumor cell, cellular response to UV, regulation of cell cycle process.

The biological pathway using the genes obtained from the meta-analysis showed, there were a total of 43 biological pathways with a p-Value ≤ 0.05. In our research, biological pathways related to lung cancer are listed in Table 3. The important pathways in lung cancer are cell adhesion molecules, PPAR signaling pathway, TNF signaling pathway, ECM-receptor interaction, p53 signaling pathway, PI3K-Akt signaling pathway, and Cell cycle.

Our results showed that if the functional processes and biological pathways mentioned in this research are changed for any reason in healthy lung tissue and lead to increased cell proliferation, invasion, and cell migration in an abnormal manner, they cause lung cancer.

Protein-protein interaction network of differentially expressed genes

Using the different expression genes obtained from meta-analysis between tumor tissue and healthy tissue, the protein-protein interaction network was drawn with the help of the String online database and Cytoscape software (Figure 2). Then, six key genes) IL6, MMP9, VWF, PECAM1, FOS, CAV1) of the important and effective in lung cancer were identified based on grade. Among these genes, IL6 gen has the greatest impact on lung cancer (Table 4). It is shown in Figure 1, the content of the experimental groups and the trend of the three groups also decreased with time, but the difference between SNL and GBP was not very large and statistically insignificant.

Discussion

Cancer stem cells are the cancer cells that can reconstruct and differentiate (34) Abnormal proliferation and migration of cancer cells are caused by numerous processes and signalling pathways that converge in the nucleus to reprogram the cellular transcriptome (35). In general, genes responsible for cell proliferation and migration have abnormal activity and more in lung cancer cells in comparison with normal cells (35). Uncontrolled proliferation and migration are common in lung cancer cells and are known for this characteristic (35). In lung cancer, the normal epithelial cells gain the ability to multiply and migrate to invade the lung, which causes cancer to progress. For new lung cancer treatments, the use of inhibitors that affect the epidermal growth factor receptor can be an effective way(36). Nuclear factor erythroid 2-related factor 2 (Nrf2), plays the important role in the control mechanisms of the cellular defense response, regulation of the antioxidant system, and regulation of endogenous antioxidants and phase II detoxification enzymes and transporters, if it is restrained, prevents the development of lung cancer. (37). In a healthy person, cells grow and die, but in cancer, we face abnormal growth of some cells (38). Some factors, including internal and environmental factors, cause cancer by causing continuous cell growth and changing the genetic structure of cells (39). Among the internal factors of abnormal cell growth and environmental factors, tobacco smoke and ultraviolet rays can be mentioned in causing

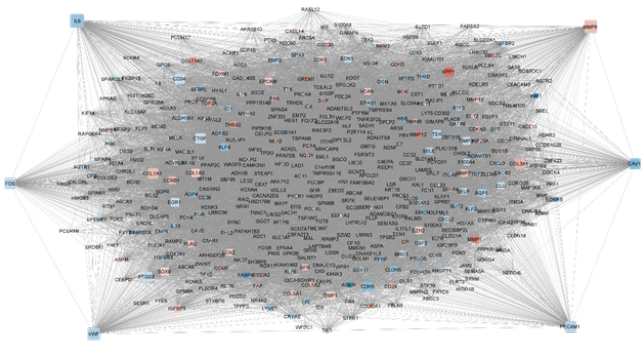

Figure 2. The PPI interaction network was constructed from 515 differentially expressed genes (DEG), the blue colour shows genes with low expression and the red colour shows genes with high expression. The size of nodes is based on the degree.

Table 2. Functional processes associated with DEGs associated with lung cancer in human.

Category	Gene Set	Description	p-Value	Gene
BP	GO:0071560	cellular response to transforming growth factor beta stimulus	1.84E-08	ACVRL1,GDF10,HPGD,PDE2A,FOS,LRRC32,TGFBR2,TGFBR3,CDH5,CLDN5,CLEC3B,COL3A1,COL1A2,HYAL2,ID1,SOX9,FERMT2
BP	GO:0048523	negative regulation of cellular process	8.40E-08	SEMA5A,ACVRL1,ADAMDEC1,HPGD,GMNN,FHL1,WFDC1,FOXM1,CLU,SOX17,MDK,ADAMTS1,HYAL1,CAMK2N1,PODXL,HYAL2,AGR2,SLIT2,ADAMTS8,CD34,JAM2,CCL23,ANGPT1,WFS1,IGFBP3,MIF,KLF4,CBFA2T3,NME1,TGFBR3,SFRP4,BMP2,IL6,CLDN3,RGCC,AGTR2,CRYAB,FERMT2,TNFRSF21,CDKN3
BP	GO:0045597	positive regulation of cell differentiation	2.90E-07	ACVRL1,CSF3,IGFBP3,ZBTB16,ADIRF,LPL,TGFBR2,COL1A1,TMEM100,ZFP36,PCP4,BMP2,IL6,RGCC,RRAS,MDK,AGTR1,SOX9,CD36,ECT2,CD34,HOXA5,FERMT2,EZH2
BP	GO:0008284	positive regulation of cell population proliferation	5.70E-07	CCL14,SLC35F6,CSF3,VIPR1,PLA2G1B,C5AR1,KIF14,TTK,FOXM1,AQP1,GRK5,EPCAM,MDK,HYAL1,CXCR2,TIMP1,SOX9,KRT6A,EDN1,EMP2,MIF,TBX3,NME1,TGFBR2,GREM1,TGFBR3,CLDN5,BMP2,IL6,MEIS1,PRC1,GAS6,IL7R,EZH2
BP	GO:0007179	transforming growth factor beta receptor signaling pathway	1.11E-06	ACVRL1,GDF10,HPGD,FOS,LRRC32,TGFBR2,TGFBR3,CDH5,CLDN5,COL3A1,COL1A2,ID1,FERMT2
BP	GO:0010604	positive regulation of macromolecule metabolic process	1.40E-06	RAMP2,RAMP3,CLU,CDH5,CDH3,HEY1,CAMK2N1,LAMP3,AGR2,SOX9,CD36,CD34,HOXA5,EGR1,IL33,ANGPT1,WFS1,PDE2A,KLF4,SELE,KLF2,GREM1,CLDN5,SFRP4,BMP2,IL6,CLDN3,RGCC,GAS6
BP	GO:0051240	positive regulation of multicellular organismal process	1.64E-06	EPAS1,ADRB2,PLAC8,GHR,ACADL,MDK,ZBED2,LEPR,SOX9,CD36,IL33,CAV1,ZBTB16,MIF,TGFBR2,COL1A1,FGR,BMP2,IL6,FABP4,RGCC,FABP5,MFAP2,LCN2,GAS6,FERMT2,EZH2
BP	GO:0007178	transmembrane receptor protein serine/threonine kinase signaling pathway	4.80E-06	ACVRL1,GDF10,HPGD,FOS,LRRC32,TGFBR2,TMEM100,TGFBR3,CDH5,CLDN5,BMP2,COL3A1,COL1A2,ID1,FERMT2
BP	GO:0071345	cellular response to cytokine stimulus	6.26E-06	CCL14,CSF3,CEBPD,STK39,AQP4,PTGS2,CXCL2,SOCS2,GHR,DUOX1,ZFP36,HYAL1,HYAL2,LEPR,S1PR1,TIMP1,SOX9,CD36,EGR1,CCL23,MME,MMP1,PDE2A,FOS,MMP9,IL6,COL1A2,LCN2,MNDA,GAS6,TNFRSF21,IL18R1
BP	GO:0048522	positive regulation of cellular process	6.74E-06	CCL14,SLC35F6,CSF3,VIPR1,RAMP3,PLA2G1B,KIF14,HBB,TTK,FOXM1,ZFP36,CDH3,GRK5,EPCAM,MDK,HYAL1,CXCR2,TIMP1,SOX9,CD36,KRT6A,EDN1,CAV1,SFTPD,EMP2,HBA1,TBX3,TGFBR2,GREM1,CLDN5,IL6,MEIS1,PRC1,FKBP1B,GAS6,IL7R,S100A8,EZH2
BP	GO:0043410	positive regulation of MAPK cascade	1.00E-05	CCL14,EDN1,CCL23,NDRG4,GPR37,RAMP3,ANGPT1,CAV2,C5AR1,MIF,ADRB2,AGER,MARCO,BMP2,IL6,S100A12,CD36,TEK,CD24,GAS6,FERMT2,EZH2
BP	GO:0071310	cellular response to organic substance	4.10E-05	ACVRL1,CSF3,RAMP2,RAMP3,MME,SLC1A1,KLF4,TGFBR2,SOCS2,GHR,CLEC3B,SLIT2,IL18R1
BP	GO:0042127	regulation of cell population proliferation	5.43E-05	CCL14,ACVRL1,SLC35F6,CSF3,VIPR1,PLA2G1B,KIF14,TTK,FOXM1,CLU,GRK5,EPCAM,ADAMTS1,CAMK2N1,CXCR2,TIMP1,SOX9,ADAMTS8,KRT6A,CCL23,EDN1,IGFBP3,EMP2,KLF4,CBFA2T3,TBX3,NME1,TGFBR2,GREM1,CLDN5,SFRP4,BMP2,IL6,MEIS1,CLDN3,RGCC,PRC1,AGTR1,IL7R,EZH2,CDKN3
BP	GO:0071635	negative regulation of transforming growth factor beta production	1.11E-04	LAPTM4B,CDH3,GATA6,CD24
BP	GO:0030856	regulation of epithelial cell differentiation	1.41E-04	CAV1,MAFF,SOX9,CD24,APOLD1

BP	GO:0071363	cellular response to growth factor stimulus	1.45E-04	ACVRL1,RAMP2,EGR3,PDE2A,NDNF,KLF4,TGFBR2,TMEM100,ZFP36,BMP2,CLEC3B,HYAL1,HYAL2,SOX9
BP	GO:0071492	cellular response to UV-A	1.70E-04	MME,MMP1,TIMP1,MMP9
BP	GO:0045596	negative regulation of cell differentiation	3.21E-04	GDF10,CAV1,ZBTB16,CRIM1,TBX3,GREM1,IL6,MEIS1,EFEMP1,COL5A1,HEY1,COL5A2,SOSTDC1,SOX9,FERMT2
BP	GO:0010224	response to UV-B	3.53E-04	MFAP4,MME,HYAL1,HYAL2
BP	GO:0008285	negative regulation of cell population proliferation	4.52E-04	ACVRL1,CCL23,NDRG4,IGFBP3,GATA6,KLF4,CBFA2T3,TBX3,NME1,GREM1,TGFBR3,SFRP4,BMP2,IL6,CLDN3,RGCC,FAP,CAMK2N1,ADAMTS1,OGN,SOX9,ADAMTS8,CDKN3
BP	GO:0070141	response to UV-A	4.83E-04	MME,MMP1,TIMP1,MMP9
BP	GO:0050679	positive regulation of epithelial cell proliferation	6.75E-04	SEMA5A,MMP12,BMP2,CDH3,EGR3,HYAL1,MDK,C5AR1,SOX9,TEK,NME1
BP	GO:0050678	regulation of epithelial cell proliferation	0.001169	ACVRL1,TGFBR3,ZFP36,ANGPT1,HYAL1,TIE1,C5AR1,SOX9,NME1
BP	GO:0034644	cellular response to UV	0.001372	MFAP4,MME,HYAL1,MMP1,HYAL2,TIMP1,MMP9,AQP1
BP	GO:0090288	negative regulation of cellular response to growth factor stimulus	0.001757	GREM1,BMP2,MMRN2,CRIM1,SOSTDC1,AGTR2,SLIT2,SULF1
BP	GO:0030858	positive regulation of epithelial cell differentiation	0.002048	TMEM100,SFRP4,SFN,SOX9
BP	GO:0090068	positive regulation of cell cycle process	0.002086	CCNB1,EDN1,RGCC,NUSAP1,KIF14,ECT2,NDC80,E2F8,MAD2L1
BP	GO:0045926	negative regulation of growth	0.002855	ACVRL1,SOX17,HYAL1,HYAL2,MT1M,FHL1,TMPRSS4,WFDC1,AGTR2,SLIT2
BP	GO:0071636	positive regulation of transforming growth factor beta production	0.00303	GATA6,PTGS2,CD34
BP	GO:2000045	regulation of G1/S transition of mitotic cell cycle	0.003641	RGCC,ADAMTS1,HYAL1,FHL1,FAM107A,KIF14,KLF4
BP	GO:0061448	connective tissue development	0.003925	HYAL1,HYAL2,ZBTB16,SOX9,SULF1
BP	GO:0050680	negative regulation of epithelial cell proliferation	0.003938	TGFBR3,RGCC,CAV2,CAV1,PTPRM,SOX9,SULF1
BP	GO:1900745	positive regulation of p38MAPK cascade	0.004112	BMP2,GADD45B,AGER,SASH1
BP	GO:0051726	regulation of cell cycle	0.004214	PPP1R15A,GADD45B,HPGD,GMNN,GATA6,MIF,FOXM1,TBX3,CCNB1,BMP2,RGCC,FAP,GRK5,CAMK2N1,SOX9,DLGAP5,CDKN3
BP	GO:0045604	regulation of epidermal cell differentiation	0.004789	SFRP4,ZFP36,MAFF,SFN
BP	GO:0070167	regulation of biomineral tissue development	0.005536	HEY1,S1PR1,SOX9,GAS6
BP	GO:0051093	negative regulation of developmental process	0.005709	GREM1,BMP2,HEY1,SOX9,MIF,FOXM1,GAS6
BP	GO:0043408	regulation of MAPK cascade	0.0071	GREM1,TGFBR3,BMP2,IL6,GPR37,RRAS,CAV2,CAV1,ADRB2,TEK,CD24
BP	GO:0014855	striated muscle cell proliferation	0.007373	TGFBR3,NDRG4
BP	GO:0046621	negative regulation of organ growth	0.007373	WWC2,SLC6A4
BP	GO:0001558	regulation of cell growth	0.00895	ACVRL1,SOX17,HYAL1,HYAL2,FHL1,SEMA3G,WFDC1,AGTR2,SLIT2
BP	GO:0090287	regulation of cellular response to growth factor stimulus	0.011026	SFRP4,SLIT2,SULF1
BP	GO:0071634	regulation of transforming growth factor beta production	0.012961	LRRC32,PTGS2,CD34
BP	GO:1901388	regulation of transforming growth factor beta activation	0.014918	GATA6,LRRC32

BP	GO:0032908	regulation of transforming growth factor beta1 production	0.014918	LAPTM4B,GATA6
BP	GO:0032909	regulation of transforming growth factor beta2 production	0.014918	CDH3,GATA6
BP	GO:0043567	regulation of insulin-like growth factor receptor signaling pathway	0.015077	BMP2,CDH3,IGFBP3
BP	GO:1902808	positive regulation of cell cycle G1/S phase transition	0.015923	RGCC,ADAMTS1,HYAL1,EZH2
BP	GO:1901990	regulation of mitotic cell cycle phase transition	0.016919	CDC20,TPX2,CCNB1,RGCC,UBE2C,CDK1,KIF14,BUB1B,NEK2,HMMR,MAD2L1
BP	GO:1900744	regulation of p38MAPK cascade	0.01923	BMP2,GADD45B,AGER,SASH1
BP	GO:0001938	positive regulation of endothelial cell proliferation	0.020686	SEMA5A,BMP2,EGR3,MDK,AGTR1,TEK
BP	GO:0007517	muscle organ development	0.022777	SGCE,EGR3,FHL1,TCF21,SGCG
BP	GO:0070848	response to growth factor	0.027037	ACVRL1,GATA6,KLF4,TGFBR2
BP	GO:0030177	positive regulation of Wnt signaling pathway	0.028239	SEMA5A,COL1A1,SFRP4,SCEL,BMP2,CDH3,CAV1,GPC3,SULF1
BP	GO:0010564	regulation of cell cycle process	0.029217	CAV2,PRC1,NEK2,SOX9,KIF20A,KIF11,ECT2
BP	GO:0002357	defense response to tumor cell	0.030244	PRF1,KLF4
BP	GO:0046620	regulation of organ growth	0.030244	WWC2,SLC6A4
BP	GO:2000026	regulation of multicellular organismal development	0.042402	SOX17,CDK1,CD24
BP	GO:0030178	negative regulation of Wnt signaling pathway	0.042626	GREM1,SFRP4,BMP2,SOX17,MDK,WIF1,CAV1,TPBG,SOSTDC1,SOX9
BP	GO:0071378	cellular response to growth hormone stimulus	0.042758	GHR,SOCS2
BP	GO:0043406	positive regulation of MAP kinase activity	0.043687	EDN1,S100A12,CD24,SASH1,EZH2

Table 3. Biological pathway associated with DEGs associated with lung cancer in human.

Databases	description	p-Value	Gene
KEGG pathway	Cell adhesion molecules	1.77E-05	ICAM2,PTPRM,SELE,SELP,CLDN22,CDH5,CLDN5,VCAN,CDH3,CLDN3,ITGA8,PECAM1,CLDN18,CD34,JAM2
KEGG pathway	AGE-RAGE signaling pathway in diabetic complications	2.27E-05	COL1A1,EGR1,THBD,IL6,EDN1,COL3A1,COL1A2,PLCB4,AGTR1,AGER,SELE,TGFBR2
KEGG pathway	Transcriptional misregulation in cancer	2.95E-05	GADD45B,HPGD,IGFBP3,ZBTB16,LMO2,DEFA3,DEFA1,IGH,MMP9,TGFBR2,FUT8,IL6,MEIS1,PLAU,TSPAN7,ERG,DEFA1B
KEGG pathway	ECM-receptor interaction	1.71E-04	COMP,COL1A1,TNXB,COL1A2,VWF,ITGA8,SPP1,CD36,HMMR,THBS2
KEGG pathway	TNF signaling pathway	0.001184905	IL6,EDN1,MAP3K8,FOS,CXCL3,PTGS2,SELE,CXCL2,MMP9,IL18R1
KEGG pathway	Cell cycle:	0.00254059	CDC20,CCNB1,PTTG1,GADD45B,CDK1,BUB1B,SFN,TTK,MCM2,MAD2L1
KEGG pathway	p53 signaling pathway	0.004253594	CCNB1,RRM2,GADD45B,SESN1,IGFBP3,CDK1,SFN
KEGG pathway	PPAR signaling pathway	0.004587587	FABP4,ACADL,FABP5,MMP1,OLR1,LPL,CD36
KEGG pathway	PI3K-Akt signaling pathway	0.022040115	CSF3,TNXB,VWF,ANGPT1,IGH,THBS2,GNG11,EFNA4,COL1A1,COMP,GHR,IL6,COL1A2,SPP1,ITGA8,TEK,IL7R
KEGG pathway	TGF-beta signaling pathway	0.048126704	GREM1,BMP2,ID1,ID4,ID3,TGFBR2

Table 4. Key genes related to lung cancer in humans.

Gene	Gene Name	Degree	Closeness	Betweenness
IL6	Interleukin 6	221.0	0.6536857	5681.051
MMP9	Matrix metalloproteinase 9	206.0	0.640327	3993.3298
VWF	von Willebrand factor	198.0	0.6300268	5028.92
PECAM1	Platelet And Endothelial Cell Adhesion Molecule 1	180.0	0.6176084	2420.1301
FOS	Fos Proto-Oncogene, AP-1 Transcription Factor Subunit	174.0	0.61277705	4044.7502
CAV1	Caveolin-1	173.0	0.61277705	4015.685

cancer (40,41). Genetic or epigenetic changes in the main regulators of the cell cycle are related to the division of cancer cells(42).

Epithelial cell adhesion molecule is expressed in different types of human cancers, such as lung cancer (43). So it can be a way to treat this disease. PPARγ regulates tumor growth, cell proliferation, and cell invasion by inactivating different signaling pathways (44). TGF causes various diseases related to cancer and their progression (45,46). Previous studies have shown that TGF is involved in the malignancy, differentiation, and metastasis of tumors, such as NSCLC (47,48). The P53 path plays an important role in the cell cycle setting (49). By regulating transcription, p53 acts as the most important tumor suppressor in human cancers (50,51). In various types of human tumors, PI3K/AKT has excessive activity (52). Based on previous studies, ECM receptor interaction plays a role in tumor invasion and metastasis (53,54). Previous findings have shown that PI3K/AKT is involved in invasion and migration in lung cancer cells (52). The cell cycle is related to the growth of cells, and it is regulated using various factors, pathways, and genes. Leaving this cycle out of the normal way causes cancer (55).

The first key gene in lung cancer is called interleukin 6 (IL6), which has the highest degree. In our research, this gene is involved in functional processes and biological pathways: negative regulation of the cellular process, positive regulation of cell differentiation, positive regulation of cell population proliferation, positive regulation of macromolecule metabolic process, positive regulation of the multicellular organismal process, cellular response to cytokine stimulus, positive regulation of the cellular process, positive regulation of MAPK cascade, regulation of cells population proliferation, negative regulation of cell differentiation, negative regulation of cell population proliferation, regulation of MAPK cascade, AGE-RAGE signaling pathway in diabetic complications, transcriptional misregulation in cancer, TNF signaling pathway, and PI3K-Akt signaling pathway. The high level of IL-6 in cancer tissue and serum indicates the progress of the disease and treatment and the poor survival of people with lung cancer (56,57). High levels of IL-6 cause damage as well as the progress of postoperative lung cancer disease.

Matrix metalloproteinase 9 (MMP9) is the second key gene related to lung cancer According to our results, this gene plays a potential role in these processes and pathways: cellular response to cytokine stimulus, cellular response to UV-A, response to UV-A, cellular response to UV, transcriptional misregulation in cancer, and TNF signaling pathway. Matrix metalloproteinases (MMP) cause damage to the extracellular matrix (ECM) and base membrane (BM) and are involved in the invasion of cancer and metastasis. Diagnosis of SNP and enzyme activity among MMP9 and MMP13 can be a method for identifying non-small cell lung cancer(58). The C allele of genetic polymorphism in the MMP-9 gene RS3918242 is a major risk factor in people with lung cancer(58). Previous findings showed that MMP-9 is expressed in healthy lung tissue, but its expression was higher in lung cancer tissue(59).

The third key gene in lung cancer is the von Willebrand factor (VWF). Our results indicated that ECM receptor interaction and PI3K-Akt signaling pathway are the pathways, in which this gene is involved. Previous studies showed that VWF is involved in tumor cell proliferation and apoptosis, and the high expression level of this gene indicates cancer progression (60). VWF disables angiogenesis and causes lung adenocarcinoma growth, VWF supplementation may be useful for treating this type of cancer (61). VWF is lowly expressed in lung cancer compared to healthy lung tissue (62).

The next key gene in lung cancer is Platelet And Endothelial Cell Adhesion Molecule 1 (PECAM-1) Our results showed, this gene plays a role in cell adhesion molecules. PECAM-1 expression has been identified in many tumor cells, including lung cancer(63,64). The correlation between the expression of PECAM-1 in lung cancer and cell adhesion, proliferation, and migration has shown that this gene is involved in the development of cancer(65). PECAM1 in lung cancer has low expression compared to healthy lung tissue (66).

Another key gene in lung cancer is Fos Proto-Oncogene, AP-1 Transcription Factor Subunit (FOS). Based on our results, this gene plays a potential role in these processes and pathways: cellular response to transforming growth factor beta stimulus, transforming growth factor beta receptor signaling pathway, transmembrane receptor protein serine/threonine kinase signaling pathway, cellular response to cytokine stimulus, TNF signaling pathway. Previous findings showed that FOS with its downregulation can play a role in the pathogenesis of lung cancer(67). This gene is a transcription factor and can self-regulate (68). The expression of FOS in lung cancer is very low compared to healthy lung tissue(69,70).

And finally, the last key gene effective in lung cancer is Caveolin-1 (CAV1). According to our reviews, this gene plays role in the positive regulation of the multicellular organismal process, positive regulation of the cellular process, regulation of epithelial cell differentiation, negative regulation of cell differentiation, negative regulation of epithelial cell proliferation, regulation of MAPK cascade, positive regulation of Wnt signaling pathway, negative regulation of Wnt signaling pathway. Abnormal expression of Cav-1 is involved in the progression of lung cancer with abnormal proliferation, migration, and apoptosis(71). The expression of Cav-1 in lung cancer is very low compared

to healthy lung tissue(71). Epidermal growth factor receptor (EGFR) is affected by Cav-1 in lung cancer (72).

Conclusions

We have identified differential expression of genes between the non-tumor and tumor tissue samples using meta-analysis. Also, among these genes, we identified genes that played a greater role in lung cancer, and we determined the processes and pathways in which these genes were involved, which can be used as markers for early detection of this type of cancer. Therefore, the identification of key genes obtained by comparing healthy individuals and cancer individuals leads us to the development of identification methods for the treatment of lung cancer.

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None

Interest conflict

The authors declare that they have no conflict of interest.

Author's contribution

H.D,X.W: have made research design;H.D,X.W: did the data collection,data analysis and drafted the paper;X.W revising and rewriting the manuscript. All the authors have approved the final version of the manuscript.

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