European Review for Medical and Pharmacological Sciences 2017; 21: 2397-2404

Identification of genes associated with lung cancer by bioinformatics analysis

J. LI[1], H. YU[1], Y.-F. MA[1], M. ZHAO[1], J. TANG[2]

[1]Department of Thoracic Surgery, General Hospital of People's Liberation Army, Beijing, China
[2]Department of Cardio-thoracic Surgery, First Affiliated Hospital of Chinese PLA General Hospital, Beijing, China

Abstract. – OBJECTIVE: This study was aimed to explore the underlying genes associated with lung cancer (LC) by bioinformatics analysis.

DATA AND METHODS: Gene expression profile GSE2514 was downloaded from the Gene Expression Omnibus database. Twenty lung and nineteen para-carcinoma tissue samples were used to identify the differentially expressed genes (DEGs) by paired t-test. Pathway enrichment analysis of DEGs was performed, followed by the construction of protein-protein interaction (PPI) network. Functional enrichment analysis of the module identified from PPI network was performed, and the enriched term with the highest enrichment scores was selected for pathway enrichment analysis.

RESULTS: Total 257 DEGs including 179 up-regulated DEGs such as monoamine oxidase A (MAOA) and intercellular adhesion molecule 2 (ICAM2), and 78 down-regulated DEGs such as thrombospondin-2 (THBS2) were identified. Up-regulated DEGs were enriched in 7 pathways, such as drug metabolism, tyrosine metabolism and cell adhesion molecules (CAMs). Down-regulated DEGs were enriched in extracellular cell matrix receptor interaction and focal adhesion pathways. In the PPI network, interleukin-6 (IL6) had the highest connectivity degree of 39. Module 1 with the highest functional enrichment scores of 5.457 containing 13 hub genes such as KIAA0101.

CONCLUSIONS: DEGs of LC were mainly enriched in the pathways related to metabolism and cell adhesion. The DEGs such as MAOA, ICAM2, IL6, THBS2 and KIAA0101 may be the potential targets for LC diagnosis and treatment.

Key Words:
Lung cancer, Molecular mechanism, Differentially expressed genes, Pathway enrichment analysis.

Introduction

Lung cancer (LC) is one of the most common fatal malignancies in economically developed countries and the second leading cause of death in developing countries[1]. More than 1 million people die of LC annually[2]. Although diagnosis at an early stage is increasing with the introduction of some novel technologies, LC is still a devastating disease which has a very poor prognosis[3]. The poor prognosis for LC patients is generally owing to the inability to treat the resultant late stage of it[4].

Numerous studies have made contributions to explore the mechanism and therapeutic method for LC. Achievements have been obtained in exploring the pathological mechanism underlying the LC development. Some genes and pathways have been found to play key roles in the LC progression. For example, somatic mutations in *p53* gene play an important role in the pathogenesis of early stage LC[5]. Amplified and increased expression of the v-*myc* avian myelocytomatosis viral oncogene homolog (*myc*) family of protooncogenes has been described to be associated with rapid proliferation in LC cells[6]. The dysregulation or deletion of one gene might affect the function of many other genes since there are complex interactions among various genes, their effectors, and the pathways in which they involve[7]. In addition, pathways have been identified to control important aspects of DNA repair and genomic stability[8]. At present, some critical pathways have been found to be related to LC, such as mitogen-activated protein kinase kinase and phosphatidyl inositol 3-kinase pathway[9]. The development of gene expression profiling technology[10] is becoming more and more important to our understanding of LC biology. Although progresses have been achieved about the pathogenesis of LC, the genetic mechanisms of LC are far from being clear.

In the present study, we downloaded GSE2514 and identified the differentially expressed genes (DEGs) between the LC and normal donors (ND)

Corresponding Author: Jian Tang, MM; e-mail: jiantangjjttd@163.com

samples to explore the molecular mechanisms of LC. Besides, we performed pathway enrichment analysis, protein-protein interaction (PPI) networks and module analysis to study and identify the target genes for diagnosis and treatment of LC. Findings of this study might play important roles in lung tumor genesis and may potentially serve as biomarkers in both diagnosis and prognosis of human LC.

Data and Methods

Affymetrix Microarray Data

The microarray expression profile dataset GSE2514[11] was downloaded from National Center of Biotechnology Information (NCBI) Gene Expression Omnibus (GEO, http://www.ncbi.nlm.nih.gov/geo/) database which is based on the GPL8300 [HG_U95Av2] Affymetrix Human Genome U95A Version 2 Array platform. The dataset contains 39 samples including 20 lung and 19 para-carcinoma tissue samples. In this paper, the samples were analyzed by bioinformatics.

Data Preprocessing and Differential Expression Analysis

The original expression data in CEL files were firstly converted into expression measures and the quartile data were normalized by robust multiarray average (RMA)[12] in R Affy package. Then the samples were divided into two groups: LC and ND. The paired *t*-test based on the limma package[13] in R was used to identify DEGs in LC and ND samples. Then log2-fold change (logFC) was calculated. Only genes with $|logFC| > 1.0$ and adjusted p-value < 0.05 were regarded as DEGs.

Pathway Enrichment Analysis of DEGs

The Database for Annotation, Visualization and Integrated Discovery (DAVID)[14] that consists of an integrated biological knowledgebase and analytic tools is used for systematic and integrative analysis of large gene protein lists. Kyoto Encyclopedia of Genes and Genomes (KEGG)[15] is a collection of online databases used for dealing with genomes, enzymatic pathways and biological chemicals. KEGG pathway enrichment analysis for the identified DEGs was performed by DAVID online tool with the threshold of p-value < 0.05.

Protein-Protein Interactions Analysis and Network Construction

The Search Tool for the Retrieval of Interacting Genes (STRING) database[16] is a precomputed global resource which has been designed to evaluate the PPI information. In this paper, the STRING online tool was applied to analyze the PPI of DEGs and only those experimentally validated interactions with a combined score > 0.4 was selected as significant.

Cytoscape[17] is a general bioinformatics package used for visualizing biological network and integrating data. PPI networks were constructed using the Cytoscape software based on the PPI relationships obtained. From the previous studies on biological network obtained, most of the PPI networks obeyed the scale-free attribution[18]. So

Table I. The enriched KEGG pathways for the up- and down-regulated DEGs.

Term	Count	*p* value
Up-regulated DEGs		
hsa04610: Complement and coagulation cascades	8	7.7E-05
hsa04270: Vascular smooth muscle contraction	9	2.8E-04
hsa00982: Drug metabolism	5	1.5E-02
hsa04514: Cell adhesion molecules (CAMs)	7	1.5E-02
hsa05416: Viral myocarditis	5	2.3E-02
hsa00350: Tyrosine metabolism	4	2.9E-02
hsa00360: Phenylalanine metabolism	3	4.4E-02
Down-regulated DEGs		
hsa04512: ECM-receptor interaction	3	1.7E-03
hsa04510: Focal adhesion	7	3.6E-02
DEGs stands for differentially expressed genes; Count stands for the number of enriched DEGs.		

DEGs stands for differentially expressed genes; Count stands for the number of enriched DEGs.

Table II. The statistical results of connectivity degrees of top 6 hub genes in PPI network.

Gene	Degree	Adj. *p* value	Gene	Degree	Adj. *p* value
IL6	39	1.7E-4	*F3*	17	1.4E-4
FOS	28	1.0E-4	*VWF*	17	1.6E-12
MMP9	24	7.1E-7	*KIAA0101*	16	3.6E-8

connectivity degree was analyzed by statistics in networks to obtain the important nodes, namely hub proteins[19] which participated in PPI relations of the networks.

Network Modeling Analysis

Clustering with overlapping neighbourhood expansion (ClusterONE)[20] is used to discover densely connected and possibly overlapping regions within the PPI network. In the current study, ClusterONE was used to analyze the PPI network with the threshold of p-value < 1.0E-5.

Gene Ontology (GO) analysis is a popular approach for functional studies of large-scale genomic or transcriptomic data[21]. In this paper, GO functional enrichment analysis (with the threshold of p-value < 0.05) and KEGG pathway database enrichment analysis of the module genes was performed by DAVID online tool and the module which had the highest enrichment score was selected for pathway enrichment analysis.

Results

Identification of DEGs and KEGG Pathway Enrichment Analysis

For dataset GSE2514, a total of 257 DEGs including 179 up-regulated such as monoamine oxidase A (*MAOA*) and intercellular adhesion molecule 2 (*ICAM2*), and 78 down-regulated DEGs such as thrombospondin-2 (*THBS2*) were selected.

The significantly enriched pathways of the up-regulated DEGs and down-regulated DEGs were shown in Table I. The up-regulated DEGs were enriched in 7 pathways such as, cell adhesion molecules (CAMs), drug metabolism and tyrosine metabolism. The down-regulated DEGs were enriched in extracellular matrix (ECM) receptor interaction and focal adhesion.

PPI Network Construction

A total of 452 PPI relationships were obtained. The PPI networks with internal nodes more than 2 were then constructedusing Cytoscape and the networks with 169 nodes and 448 edges were obtained (Figure 1). The genes interleukin-6 (*IL6*) (degree = 39), FBJ murine osteosarcoma viral oncogene homolog (*FOS*) (degree = 28), matrix metallopeptidase 9 (degree = 24), coagulation factor III (degree = 17), von Willebrand factor (degree = 17) and *KIAA0101* (degree = 16) were selected as top 6 hub nodes (Table II).

Module Analysis

Module 1 had 13 nodes and 70 edges (Figure 2). After GO functional enrichment analysis of module 1, three enriched terms were obtained and their functional enrichment scores were 5.457, 2.384 and 1.998. The enriched terms with the highest enrichment score (5.457) was related to cell cycle. The other two enriched terms were related to nucleotide binding and cellular component respectively (Table III).

Discussion

The analysis of gene expression profile revealed the underlying gene activity changes related to LC and enabled the identification of targets for management policy. In the present study, a total of 257 DEGs were identified between LC and ND samples through gene expression profile of GSE2514. The up-regulated DEGs were enriched in the pathways related to metabolism and cell adhesion, such as drug metabolism, tyrosine metabolism and CAMs, while the down-regulated DEGs were enriched in ECM receptor interaction and focal adhesion. In the PPI network, *IL6* had the highest connectivity degree. Module 1 contained 13 hub genes such as *KIAA010*1. This result suggested that these genes and pathways may play an important role in the progression of LC.

A previous study of the RNA-seq analysis showed that the DEGs between lung cancer smoker and normal controls were mainly involved in cellular processes, which suggested that smoking might influence the normal cellar process and contributed to lung cancer progres-

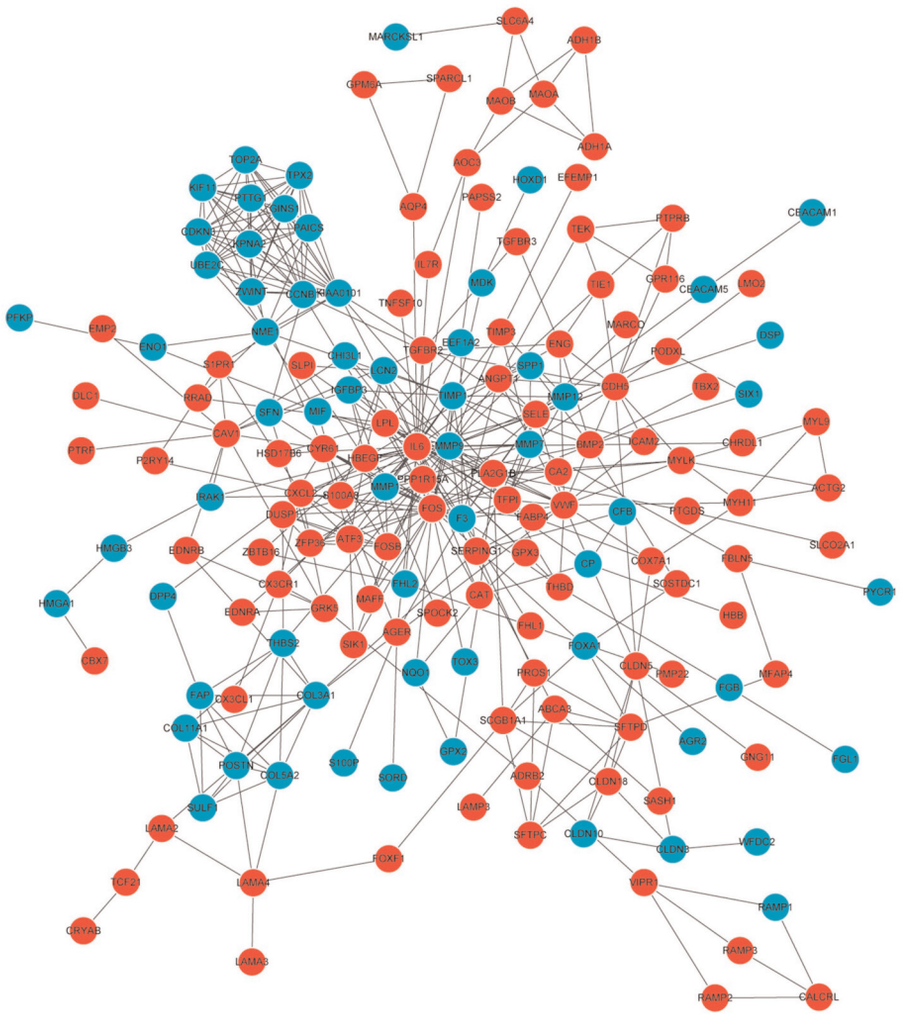

Figure 1. Interaction of proteins. Green: up-regulated DEGs; red: down-regulated DEGs.

sion[22]. Another microarray data analysis for lung cancer indicated that DEGs were enriched in functions such as cell cycle, DNA replication and immune function[23]. In our work, we obtained the similar results that cell cycle was the significant GO term that represented by DEGs in modular 1. Thus, the normal cell cycle was dysregulated in the development of lung cancer.

Additionally, it has been confirmed that genes and proteins involved in cellular metabolism played a crucial role in the development and progression of cancer[24]. In this study, *MAOs* enriching in several metabolism signaling pathways such as drug metabolism, tyrosine metabolism were up-regulated. MAOs are flavoprotein enzymes located in the mitochondrial outer membranes. Their substrates include dietary amines and neurotransmitters which are biogenic monoamines. Recent evidence supports that neurotransmitters can influence tumor growth and progression[25]. The enzymes have 2 forms, MAOA and MAOB. MAOA preferentially oxidizes serotonin and norepinephrine, whereas MAOB has a greater affinity for benzylamine and phenylethylamine. Dopamine is a common substrate of MAOA and MAOB[26]. Dopamine can inhibit tumour growth by interfering with vascular endothelial growth factor signaling in endothelial cells and blocking its angiogenic functions[27]. MAOA produces a by-product, hydrogen peroxide which is a major source of reactive oxygen species (ROS)[28]. ROS can causes DNA damage and tumor initiation and progression[29]. Kaminski et al[30] investigated MAOs in serum of patients

Table III. GO functional enrichment analysis of module 1.

Category	Term	Description	Count	*p* value
BP	GO:0000278	Mitotic cell cycle	8	3.3E-09
BP	GO:0022403	Cell cycle phase	8	7.1E-09
BP	GO:0022402	Cell cycle process	8	6.1E-08
BP	GO:0000279	M phase	7	8.2E-08
BP	GO:0000280	Nuclear division	6	4.6E-07
MF	GO:0005524	ATP binding	6	1.6E-03
MF	GO:0032559	Adenyl ribonucleotide binding	6	1.7E-03
MF	GO:0030554	Adenyl nucleotide binding	6	2.2E-03
MF	GO:0001883	Purine nucleoside binding	6	2.3E-03
MF	GO:0001882	Nucleoside binding	6	2.4E-3
CC	GO:0015630	Microtubule cytoskeleton	5	5.7E-04
CC	GO:0044430	Cytoskeletal part	5	4.5E-03
CC	GO:0005813	Centrosome	3	1.3E-02
CC	GO:0005815	Microtubule organizing center	3	1.6E-02
CC	GO:0005856	Cytoskeleton	5	1.7E-02

Category stands for the GO functional category; BP stands for biological process; MF stands for molecule function; CC stands for cellular components.

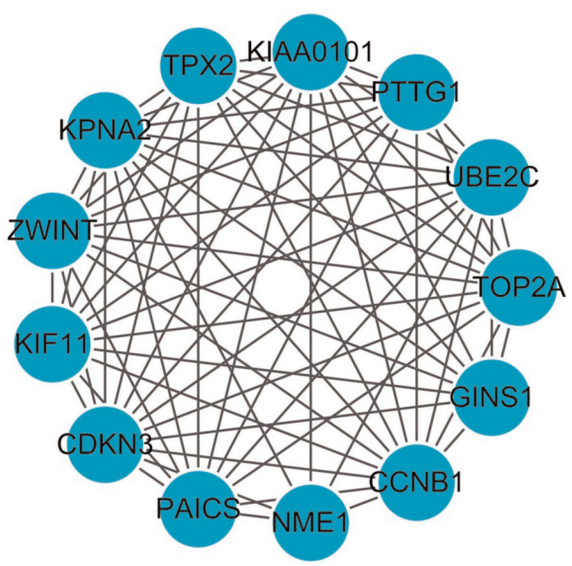

Figure 1. Module 1 with the highest MCODE score selected from PPI network.

with LC and found that the MAOs activities of serum increased notably in some cases of LC. We also found that up-regulated DEGs were enriched in the CAMs pathways. CAMs belonging to the integrin, cadherin and immunoglobulin superfamily play a key role in cell-cell adhesion, and a number of these molecules have been implicated in cancer progression and metastasis[31]. The cellular processes are modulated by the interaction of cells with each other and with their microenvironment. In normal tissue, CAM expression is tightly regulated. However, deregulation of CAMs disrupts normal cell-cell and cell-matrix interactions, which results in freeing cells from normal check points and constraints, and facilitating tumour formation and metastasis[32]. In this study, *ICAM2* enriched in CAMs signaling pathway was up-regulated. ICAM2 is a member of immunoglobulin families. Another member, ICAM1 has been reported to be associated with primary tumors and metastases and interfering with its expression inhibits experimental metastasis by melanomas in nude mice[32]. ICAM2 has structural and functional homology to ICAM1[33]. As a cell surface adhesion protein involved in leukocyte recruitment, ICAM2 is expressed at low levels on most leukocytes including T and B lymphocytes[34]. Recent gene expression profiling indicated that patients with large B cell lymphomas presented an elevated expression of ICAM2[35].

In this study, down regulated DEGs such as thrombospondin-2 (*THBS2*) were found to enrich in the ECM-receptor interaction pathways. ECM is a complex structure formed by distinct molecular networks which interact with specific cell receptors[36]. It has been demonstrated to play a crucial role in cell proliferation, migration, differentiation, apoptosis as well as carcinogenesis[37]. The protein encoded by *THBS2* has been shown to mediate cell-to-cell and cell-to-matrix interactions and inhibit the angiogenic activity, mitogenesis and formation of focal adhesions in endothelial cells[38]. This protein has been shown to function as

a potent inhibitor of tumor growth and angiogenesis[39]. Alvarez et al[40] suggested that the reduction of THBS2 expression may be coupled with the development of a malignant phenotype. Czekierdowski et al[38] reported the down-regulated expression of *THBS2* gene in ovarian cancer. In conclusion, metabolism, cell adhesion and ECM-receptor interaction signaling pathways were closely associated with LC. As a result, DEGs related to these pathways may be used as potential targets for LC treatment.

A recent study for screening lung cancer related genes with RNA-seq indicated that IL6 was a significant DEG between smokers with lung cancer and normal smokers[22]. It is consistent with our results that *IL6 as a significant* DEG was also a hub gene with the highest connectivity degree of 39 in PPI network. IL6 is a multifunctional cytokine which functions in defense response, cell survival, proliferation and apoptosis[41]. It is reported that IL6 and its major effector signal transducer and activator of transcription 3 play a central role in the epigenetic switch from non-transformed epithelia to cancer cells[42]. Yanagawa et al[43] found that patients with LC have elevated levels of IL6 and its expression is related with poor prognosis of lung cancer patients. IL6 is expressed by LC cells and acts in an autocrine or paracrine mechanisms to stimulate cancer cell proliferation and migration[44]. Taken together, these data suggest that IL6 may be a candidate molecular marker associated with LC.

In addition, we also found KIAA0101 was a hub gene in the PPI network with a higher connectivity degree of 16. Module analysis of the PPI network revealed that KIAA0101 was also enriched in module 1. KIAA0101 is a proliferating cell nuclear antigen (PCNA) associated factor and was identified as $p15^{PAF}$ in 2001[45]. PCNA is an essential scaffold molecule for DNA repair through interactions with several DNA replication proteins[46,47]. In mammalian cells, the over-expression of KIAA0101 is found to protect cells from UV-induced cell death, which supports that KIAA0101 participates in the regulation of DNA repair, apoptosis and cell cycle progression[48]. In recent years, several reports have demonstrated that the over-expression of KIAA0101 occurred in a variety of human malignancies including LC and involved in tumor progression[49,50]. Cancer patients with elevated KIAA0101 expression show a higher recurrence rate and significantly declined survival rate[51]. The over-expressed KIAA0101 has the potential to facilitate cell proliferation under both physiological conditions and human cancers, such as LC and thyroid carcinoma[52,53]. Besides, the elevated KIAA0101 level was concerned with more advanced tumor stages so the assessment of KIAA0101 expression may be helpful in determining the most appropriate duration and intensity of treatment[51].

Conclusions

Our data provide a comprehensive bioinformatics analysis of DEGs which may be involved in LC. The findings in current work may contribute to our understanding of the underlying molecular mechanisms of LC. DEGs such as *MAOA*, *ICAM2*, *THBS2*, *IL6 and KIAA0101* have the potential to be used as targets for LC diagnosis and treatment.

However, this study has a few limitations. In the process of data analysis, only a few cases of adenocarcinoma of lung and para-carcinoma tissue samples based on one platform were used for the analyses. This may cause a high rate of false positive result. Further genetic investigations with larger sample size are still needed to confirm our observation.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Mathers C, Fat DM, Boerma J. The global burden of disease: 2004 update. World Health Organization, 2008.

2) Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011; 61: 69-90.

3) National Lung Screening Trial Research Team, Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, Gareen IF, Gatsonis C, Marcus PM, Sicks J. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011; 365: 395-409.

4) Stearman RS, Dwyer-Nield L, Zerbe L, Blaine SA, Chan Z, Bunn Jr PA, Johnson GL, Hirsch FR, Merrick DT, Franklin WA, Baron AE, Keith RL, Nemenoff RA, Malkinson AM, Geraci MW. Analysis of orthologous gene expression between human pulmonary adenocarcinoma and a carcinogen-induced murine model. Am J Pathol 2005; 167: 1763-1775.

5) Chiba I, Takahashi T, Nau M, d'Amico D, Curiel D, Mitsudomi T, Buchhagen D, Carbone D, Piantadosi S, Koga H, et al. Mutations in the p53 gene are

frequent in primary, resected non-small cell lung cancer. Lung cancer study group. Oncogene 1990; 5: 1603-1610.

6) Funa K, Steinholtz L, Nou E, Bergh J. Increased expression of N-myc in human small cell lung cancer biopsies predicts lack of response to chemotherapy and poor prognosis. Am J Clin Pathol 1987; 88: 216-220.

7) Bonner AE, Lemon WJ, Devereux TR, Lubet RA, You M. Molecular profiling of mouse lung tumors: association with tumor progression, lung development, and human lung adenocarcinomas. Oncogene 2003; 23: 1166-1176.

8) Hoeijmakers JH. Genome maintenance mechanisms for preventing cancer. Nature 2001; 411: 366-374.

9) Herbst RS, Heymach JV, Lippman SM. Lung cancer. N Engl J Med 2008; 359: 1367-1380.

10) Alberg AJ, Samet JM. Epidemiology of lung cancer. Chest J 2003; 123(1 Suppl): 21S-49S.

11) Bowen NJ, Walker LD, Matyunina LV, Logani S, Totten KA, Benigno BB, McDonald JF. Gene expression profiling supports the hypothesis that human ovarian surface epithelia are multipotent and capable of serving as ovarian cancer initiating cells. BMC Med Genomics 2009; 2: 71.

12) Irizarry RA, Hobbs B, Collin F, Beazer-Barclay YD, Antonellis KJ, Scherf U, Speed TP. Exploration, normalization, and summaries of high density oligonucleotide array probe level data. Biostatistics 2003; 4: 249-264.

13) Diboun I, Wernisch L, Orengo CA, Koltzenburg M. Microarray analysis after RNA amplification can detect pronounced differences in gene expression using limma. BMC Genomics 2006; 7: 252.

14) Da Wei Huang BTS, Lempicki RA. Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. Nat Protoc 2008; 4: 44-57.

15) Wixon J, Kell D. Website review: The Kyoto encyclopedia of genes and genomes—KEGG. Http://www. Genome. Ad. Jp/kegg. Yeast 2000; 17: 48-55.

16) Von Mering C, Huynen M, Jaeggi D, Schmidt S, Bork P, Snel B. STRING: a database of predicted functional associations between proteins. Nucleic Acids Res 2003; 31: 258-261.

17) Smoot ME, Ono K, Ruscheinski J, Wang PL, Ideker T. Cytoscape 2.8: new features for data integration and network visualization. Bioinformatics 2011; 27: 431-432.

18) Junker BH, Koschützki D, Schreiber F. Exploration of biological network centralities with CentiBiN. BMC Bioinformatics 2006; 7: 219.

19) Lamb J, Crawford ED, Peck D, Modell JW, Blat IC, Wrobel MJ, Lerner J, Brunet JP, Subramanian A, Ross KN, Reich M, Hieronymus H, Wei G, Armstrong SA, Haggarty SJ, Clemons PA, Wei R, Carr SA, Lander ES, Golub TR. The connectivity map: Using gene-expression signatures to connect small molecules, genes, and disease. Science 2006; 313: 1929-1935.

20) Nepusz T, Yu H, Paccanaro A. Detecting overlapping protein complexes in protein-protein interaction networks. Nat Methods 2012; 9: 471-472.

21) Ashburner M, Ball CA, Blake JA, Botstein D, Butler H, Cherry JM, Davis AP, Dolinski K, Dwight SS, Eppig JT, Harris MA, Hill DP, Issel-Tarver L, Kasarskis A, Lewis S, Matese JC, Richardson JE, Ringwald M, Rubin GM, Sherlock G. Gene ontology: tool for the unification of biology. The Gene Ontology Consortium. Nat Genet 2000; 25: 25-29.

22) Zhou C, Chen H, Han L, Xue F, Wang A, Liang YJ. Screening of genes related to lung cancer caused by smoking with RNA-seq. Eur Rev Med Pharmacol Sci 2014; 18: 117-125.

23) Wu Q, Min J, Jiang L, Li J, Yao K. Screening of biomarkers for lung cancer with gene expression profiling data. Eur Rev Med Pharmacol Sci 2013; 17: 3221-3228.

24) Pettazzoni P, Ciamporcero E, Medana C, Pizzimenti S, Dal Bello F, Minero VG, Toaldo C, Minelli R, Uchida K, Dianzani MU, Pili R, Barrera G. Nuclear factor erythroid 2-related factor-2 activity controls 4-hydroxynonenal metabolism and activity in prostate cancer cells. Free Radic Biol Med 2011; 51: 1610-1618.

25) Hodorova I, Rybarova S, Vecanova J, Solar P, Domorakova I, Adamkov M, Mihalik J. Comparison of expression pattern of monoamine oxidase a with histopathologic subtypes and tumour grade of renal cell carcinoma. Med Sci Monit 2012; 18: BR482-6.

26) Shih JC, Chen K, Ridd MJ. Monoamine oxidase: from genes to behavior. Ann Rev Neurosci 1999; 22: 197.

27) Tilan J, Kitlinska J. Sympathetic Neurotransmitters and Tumor Angiogenesis-Link between Stress and Cancer Progression. J Oncol 2010; 2010: 539706.

28) Shih JC, Wu JB, Chen K. Transcriptional regulation and multiple functions of MAO genes. J Neural Transm 2011; 118: 979-986.

29) Trachootham D, Alexandre J, Huang P. Targeting cancer cells by ROS-mediated mechanisms: a radical therapeutic approach? Nat Rev Drug Discov 2009; 8: 579-591.

30) Kami ski K, Bodziony J, Kozielski J. Monitoring treatment of pulmonary carcinomas by serial determination of monoamine oxidase and diamine oxidase in blood serum. Archiv fur Geschwulstforschung 1983; 54: 377-385.

31) Wai Wong C, Dye DE, Coombe DR. The role of immunoglobulin superfamily cell adhesion molecules in cancer metastasis. Int J Cell Biol 2012; 2012: 340296.

32) Johnson JP. Cell adhesion molecules in the development and progression of malignant melanoma. Cancer Metastasis Rev 1999; 8: 345-357.

33) Staunton DE, Dustin ML, Springer TA. Functional cloning of ICAM-2, a cell adhesion ligand for LFA-1 homologous to ICAM-1. Nature 1989; 339: 61-64.

34) de Fougerolles AR, Stacker SA, Schwarting R, Springer TA. Characterization of ICAM-2 and evidence for a third counter-receptor for LFA-1. J Exp Med 1991; 174: 253-267.

35) Alizadeh AA, Eisen MB, Davis RE, Ma C, Lossos IS, Rosenwald A, Boldrick JC, Sabet H, Tran T, Yu X, Powell JI, Yang L, Marti GE, Moore T, Hudson J Jr, Lu L, Lewis DB, Tibshirani R, Sherlock G, Chan WC, Greiner TC, Weisenburger DD, Armitage JO, Warnke R, Levy R, Wilson W, Grever MR, Byrd JC, Botstein D, Brown PO, Staudt LM. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature 2000; 403: 503-511.

36) Aumailley M, Gayraud B. Structure and biological activity of the extracellular matrix. J Mol Med 1998; 76: 253-265.

37) Zhu XL, Ai ZH, Wang J, Xu YL, Teng YC. Weighted gene co-expression network analysis in identification of endometrial cancer prognosis markers. Asian Pac J Cancer Prev 2012; 13: 4607-4611.

38) Czekierdowski A, Czekierdowska S, Danilos J, Czuba B, Sodowski K, Sodowska H, Szymanski M, Kotarski J. Microvessel density and CpG island methylation of the THBS2 gene in malignant ovarian tumors. J Physiol Pharmacol 2008; 59(Suppl 4): 53-65.

39) THBS H, Kit TE. Mybiosource. Com.

40) Alvarez AA, Axelrod JR, Whitaker RS, Isner PD, Bentley RC, Dodge RK, Rodriguez GC. Thrombospondin-1 expression in epithelial ovarian carcinoma: Association with p53 status, tumor angiogenesis, and survival in platinum-treated patients. Gynecol Oncol 2001; 82: 273-278.

41) Kitamura A, Hasegawa G, Obayashi H, Kamiuchi K, Ishii M, Yano M, Tanaka T, Yamaguchi M, Shigeta H, Ogata M, Nakamura N, Yoshikawa T. Interleukin-6 polymorphism (-634C/G) in the promotor region and the progression of diabetic nephropathy in type 2 diabetes. Diabetic Med 2002; 19: 1000-1005.

42) Iliopoulos D, Hirsch HA, Struhl K. An epigenetic switch involving NF-kappaB, Lin28, Let-7 MicroRNA, and IL6 links inflammation to cell transformation. Cell 2009; 139: 693-706.

43) Seike M, Yanaihara N, Bowman ED, Zanetti KA, Budhu A, Kumamoto K, Mechanic LE, Matsumoto S, Yokota J, Shibata T, Sugimura H, Gemma A, Kudoh S, Wang XW, Harris CC. Use of a cytokine gene expression signature in lung adenocarcinoma and the surrounding tissue as a prognostic classifier. J Natl Cancer Inst 2007; 99: 1257-1269.

44) Yanagawa H, Sone S, Takahashi Y, Haku T, Yano S, Shinohara T, Ogura T. Serum levels of interleukin 6 in patients with lung cancer. Br J Cancer 1995; 71: 1095-1098.

45) Yu P, Huang B, Shen M, Lau C, Chan E, Michel J, Xiong Y, Payan DG, Luo Y. p15(PAF), a novel PCNA associated factor with increased expression in tumor tissues. Oncogene 2001; 20: 484-489.

46) Hosokawa M, Takehara A, Matsuda K, Eguchi H, Ohigashi H, Ishikawa O, Shinomura Y, Imai K, Nakamura Y, Nakagawa H. Oncogenic role of KIAA0101 interacting with proliferating cell nuclear antigen in pancreatic cancer. Cancer Res 2007; 67: 2568-2576.

47) Turchi L, Fareh M, Aberdam E, Kitajima S, Simpson F, Wicking C, Aberdam D, Virolle T. ATF3 and p15PAF are novel gatekeepers of genomic integrity upon UV stress. Cell Death Differ 2009; 16: 728-737.

48) Simpson F, Lammerts van Bueren K, Butterfield N, Bennetts JS, Bowles J, Adolphe C, Simms LA, Young J, Walsh MD, Leggett B, Fowles LF, Wicking C. The PCNA-associated factor KIAA0101/p15(PAF) binds the potential tumor suppressor product p33ING1b. Exp Cell Res 2006; 312: 73-85.

49) Kato T, Daigo Y, Aragaki M, Ishikawa K, Sato M, Kaji M. Overexpression of KIAA0101 predicts poor prognosis in primary lung cancer patients. Lung Cancer 2012; 75: 110-118.

50) Kais Z, Barsky SH, Mathsyaraja H, Zha A, Ransburgh DJ, He G, Pilarski RT, Shapiro CL, Huang K, Parvin JD. KIAA0101 interacts with BRCA1 and regulates centrosome number. Mol Cancer Res 2011; 9: 1091-1099.

51) Zhu K, Diao D, Dang C, Shi L, Wang J, Yan R, Yuan D, Li K. Elevated KIAA0101 expression is a marker of recurrence in human gastric cancer. Cancer Sci 2013; 104: 353-359.

52) Petroziello J, Yamane A, Westendorf L, Thompson M, McDonagh C, Cerveny C, Law CL, Wahl A, Carter P. Suppression subtractive hybridization and expression profiling identifies a unique set of genes overexpressed in non-small-cell lung cancer. Oncogene 2004; 23: 7734-7745.

53) Mizutani K, Onda M, Asaka S, Akaishi J, Miyamoto S, Yoshida A, Nagahama M, Ito K, Emi M. Overexpressed in anaplastic thyroid carcinoma-1 (OEATC-1) as a novel gene responsible for anaplastic thyroid carcinoma. Cancer 2005; 103: 1785-1790.