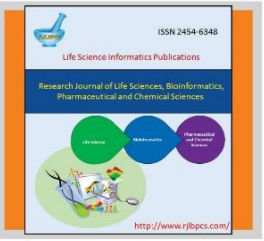

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BIOINFORMATICS ANALYSIS OF A PROGNOSTIC miRNA SIGNATURE AND POTENTIAL KEY GENES IN SMALL CELL LUNG CANCER

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ABSTRACT: Small-cell lung cancer (SCLC) is a subtype of lung cancer, accounting for approximately 15% of lung cancers, with early metastasis, high recurrence and poor prognosis. The underlying molecular mechanisms are still unclear and further research is required. The aim of the present study was to identify SCLC-specific biomarkers by evaluating the differential expression of mRNA and microRNA (miRNA) profiling of tissue from patients with SCLC and to compare the normal lung tissue. A non-coding RNA sequence dataset (GSE19945) and transcriptome sequencing dataset (GSE6044) were downloaded from the Gene Expression Omnibus (GEO) database. Using the R limma software package and the GEO2R tool of the GEO, we identified 445 differentially expressed genes (DEGs) and 128 differentially expressed miRNAs (DEmiRNAs). The GO function was significantly enriched for 26 terms, and the Kyoto Encyclopedia of Genes and Genomes (KEGG) database had fifteen enrichment pathways, mainly related to DNA replication, cell cycle, and oocyte meiosis mismatch repair. Cytoscape software was used to generate the protein-protein interaction (PPI) networks to identify the molecular mechanisms of key signalling pathways and cellular activities in SCLC. Using miRNAWalk, we identified 598 target genes of the 13, 80 miRNAs and constructed miRNA target networks. In total, there were eighteen overlapping genes regulated by 28 miRNAs between target genes of the DEmiRNAs and DEGs. The identified hub genes are important because they may be used as biomarkers for prognosis, diagnosis and therapeutic target for SCLC.

Keywords: Small-cell lung cancer, miRNA, biomarkers, Gene Expression Omnibus, protein-protein interaction.

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1. INTRODUCTION

Lung cancer is one of the most common malignant neoplasms with high morbidity and mortality rates worldwide[1]. Small cell lung cancer (SCLC) is a neuroendocrine lung cancer characterized by strong invasiveness, early metastasis, poor patient survival, and high recurrence and mortality rates, accounting for approximately 15% of bronchogenic carcinomas and up to 25% of lung cancer deaths[2,3]. Although improvement has been achieved over the last few decades, the prognosis for SCLC patients remains poor, and patients with SCLC have no obvious benefit from the current molecular targeted therapy [4]. Patients with SCLC have a dismal prognosis, with a 5-year survival rate of approximately 2% for advanced stage (metastatic) disease, which comprises 68% of cases at early diagnosis[5]. SCLC patients are resistant to conventional treatment. The high recurrence rate is due to its high mutation rate and genomic instability[6]. A previous study demonstrated that RB transcriptional corepressor 1 (RB1) and TP53 were the most commonly mutated genes in SCLC[7]. Aberrant MYC family, SOX2 and fibroblast growth factor receptor 1 activity, resulting from chromosomal translocations, gene amplification or increased mRNA/protein stability, is found in patients with SCLC[8]. MicroRNAs (miRNAs) are endogenous single-stranded non-coding RNAs, ~20-25 nucleotides in length that negatively regulate gene expression via specifically bind to target mRNA to inhibit post- transcriptional gene expression[9]. Through this mechanism, miRNAs are involved in the progression of various biological processes such as tumor cell proliferation, apoptosis, cell cycle and differentiation, and DNA repair[10]. Many studies over the past decades have shown that miRNAs are aberrantly expressed in various types of cancer including SCLC, and dysregulation of miRNAs appears to play an important role in cancer pathogenesis where they exert their effect as oncogenes or as tumour suppressors[11,12]. The expression levels of miR-25 were significantly high in SCLC and act as an oncogenic regulator[13]. Decreased expression of miR- 126 promoted activation of vascular endothelial growth factor A (VEGF) in lung cancer, thereby regulating angiogenesis[14]. In the present study, the Gene Expression Omnibus (GEO) database and comprehensive bioinformatics analysis were used to explore the differential expression of genes and miRNAs in SCLC tumor tissue and adjacent normal lung tissue samples and the potential molecular mechanisms associated with them.

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2. MATERIALS AND METHODS

MiRNA and gene microarrays

The expression profile dataset was retrieved from the Gene Expression Omnibus (GEO) (http://www.ncbi.nlm.nih.gov/geo/) database, an online public genomic database containing the entire gene expression data, chips and microarrays. To examine gene expression across human SCLC samples, the following 2 SCLC datasets were downloaded from GEO: GSE19945 and GSE6044. The miRNA expression profiles from the GSE19945 dataset, which included 43 NSCLC surgical samples and 8 normal lung tissue samples. The Agilent Human 0.6K miRNA Microarray G4471A platform was used to determine miRNA expression. The mRNA GSE6044 dataset includes samples from 9 SCLC samples and 5 normal lung tissue, which were analyzed using the GPL201 [HG- Focus] Affymetrix Human HG- Focus Target Array platform.

Screening for DE-miRNAs and DE-genes

The raw data of GSE6044 were normalized using the Affy package pair in R, using correction, normalization and log2 conversion. The analysis of differential expression of miRNAs and gene was conducted using the LIMMA software in the Bioconductor package (http://www.bioconductor.org/). The DE-miRNAs and DE-genes in SCLC tissue samples compared to normal lung tissue samples were confirmed using the GEO2R application from GEO. False Discovery Rate (FDR) corrected P-value<.05 and log fold change (FC)>1 were set as the thresholds for identifying DE-miRNAs and DE-genes. The high or low expressed DE-miRNAs and DE-genes were sorted according to the size of their FC.

Functional enrichment analysis of DEGs

In this study DAVID (https://david.ncifcrf.gov/) was used for data annotation analysis and DE-genes were subjected to molecular function and pathway studies by GO analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis.

Construction of protein- protein interaction (PPI) networks and module research

The protein-protein interaction (PPI) network of DEGs was constructed using Cytoscape software (version 3.6.0; www. cytoscape.org) to identify the molecular mechanisms of key signalling pathways and cellular activities in SCLC. An interaction score greater than 0.4 was considered to identify statistically significant PPIs. Then, the association between the genes was analyzed using the Network Analyzer plug- in tool of Cytoscape and the hub genes were confirmed by molecular complex detection (MCODE). The thresholds for screening were: degree cutoff=2', 'node score cutoff=0.2', 'k- core=2' and 'max·depth=100'.

Prediction of target genes for DE-miRNAs

The potential target genes of the DEmiRNAs were identified from online software including miRTarBase(http://mirtarbase.mbc.nctu.edu.tw), TargetScan (http://www.targetscan.org) and

miRDB (http://mirdb.org), miRTarBase (https://bio.tools/mirtarbase), and miRWalk (http://mirwalk.umm.uni-heidelberg.de/) and the miRNA target exists in the five databases concurrently were included. FunRich is a stand-alone software tool that was used to find overlapping genes between DEGs and predictive genes of DE-miRNAs. The candidate miRNA-gene negative regulatory network is generated and visualized using Cytoscape software.

3. RESULTS AND DISCUSSION

Identification of DE-miRNAs and DE-genes

When comparing patients with SCLC versus normal lung tissue samples, we identified 451 DEGs in the GSE6044 dataset, of which 205 were down-regulated and 246 were up-regulated. The p-value of 20 DEGs is shown in Table I. In total, 134 DE-miRNAs were detected in SCLC tissue samples, of which the expression of 86 was high and 49 expression was low. The 20 DE-miRNAs are shown in Table II.

Table 1. The twenty superior genes differentially expressed in SCLC compared with adjacent normal lung tissues.

Gene name	Adjusted P-value	Log FC
TMSB15	$2.22x10^{-3}$	4.6
MEST	$3.10x10^{-3}$	3.78
UCHL1	$3.28x10^{-2}$	3.08
TYMS	$3.31x10^{-2}$	2.88
TOP2A	$3.51x10^{-3}$	2.75
CDKN2A	$1.65x10^{-4}$	2.33
MCM6	$3.12x10^{-4}$	2.32
SOX4	$3.13x10^{-4}$	2.24
ACAA2	$1.97x10^{-4}$	2.12
MARCKSL1	$2.26x10^{-3}$	2.1
ID4	$3.24x10^{-3}$	1.99
IL17RB	$1.23x10^{-4}$	1.49
HDAC2	$3.55x10^{-4}$	1.39
CYP2J2	$3.16x10^{-4}$	-1.13
PDLIM4	$3.17x10^{-4}$	-1.41
FABP6	$1.66x10^{-4}$	-1.78
CES1	$3.24x10^{-3}$	-2.51
TSPAN8	$3.34x10^{-4}$	-2.94
CYP4B1	$3.44x10^{-4}$	-3.34
GSTA1	$3.54x10^{-4}$	-4.26

Table 2. Top 20 DEMs between SCLC tissues compared with normal lung tissues.

miRNAs	Adjusted P-value	Log FC
miR-7	$4.88x10^{-9}$	5.67
miR-183	$7.78x10^{-13}$	4.57
miR-130b	$1.89x10^{-13}$	4.22
miR-301b	$2.78x10^{-11}$	3.91
miR-96	$1.55x10^{-13}$	3.82
miR-182	$2.45x10^{-9}$	3.72
miR-18a	$3.54x10^{-9}$	3.35
miR-26a	$7.67x10^{-8}$	-1.82
miR-26b	$2.67x10^{-7}$	-1.92
miR-140-5p	$3.55x10^{-7}$	-1.99
miR-498	$4.57x10^{-7}$	-2.22
miR-140-3p	$3.22x10^{-7}$	-2.4
miR-638	$3.65x10^{-9}$	-2.93
miR-126	$1.45x10^{-11}$	-3.77
miR-338-3p	$2.54x10^{-7}$	-3.79
miR-145	$6.35x10^{-7}$	-3.88
miR-486-5p	$2.25x10^{-7}$	-4.04
miR-451	$3.34x10^{-8}$	-4.22
miR-144	$5.56x10^{-7}$	-4.61

GO analysis of DEGs

The functional annotation tool of DAVID (Database for Annotation, Visualization and Integrated Discovery, http://david.abcc.ncifcrf.gov/home.jsp) was used for functional enrichment analysis of the DEGs. As a result, a total of 421 DEGs were mapped to 403 GO terms. GO terms with Fisher test FDR corrected <0.05 were considered as significant enrichment, 28 significant enriched functional clusters were screened (Figure 1). The enriched GO term analysis of the identified DEGs showed that 13 GO terms were significantly enriched in cellular components, mainly involving nuclear components, including ‘nucleus’, ‘nucleoplasm’, ‘spindle’, ‘chromosome’ and ‘kinetochore’ and 11 GO terms were significantly enriched in ‘G1/S transition of mitotic cell cycle’, ‘cell division’, ‘mitotic nuclear division’, ‘DNA replication, ‘mitotic sister chromatid segregation, ‘sister chromatid cohesion, ‘positive regulation of cell proliferation and ‘DNA replication initiation, belonged to biological processes. In addition, four molecular functions were enriched, mainly involving binding related terms, such as ‘protein binding’, ‘calcium-dependent protein binding’ and ‘damaged DNA binding’.

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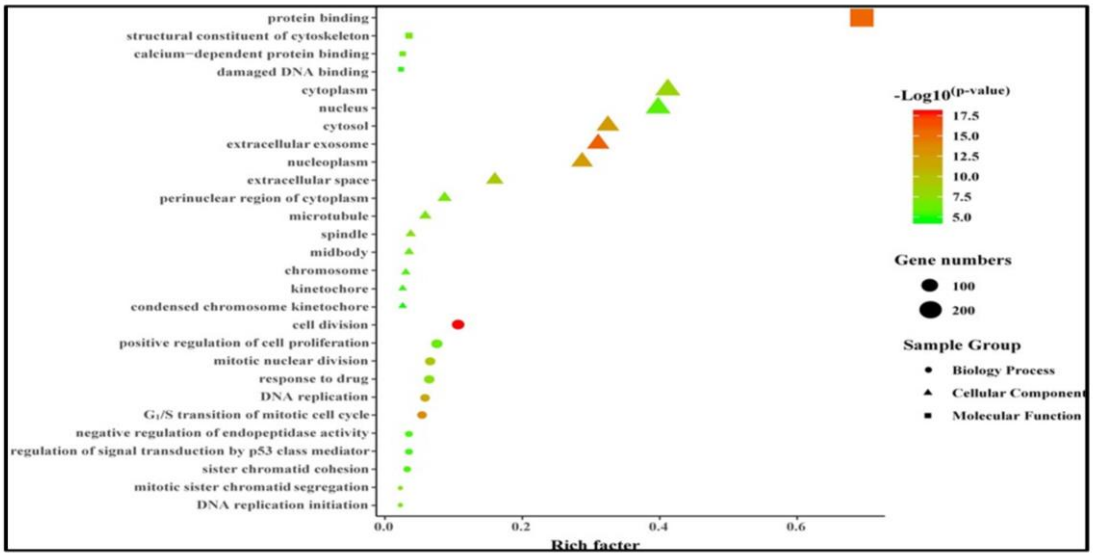

Figure 1. Gene Ontology analysis of differentially expressed genes.

Pathway analysis of DEGs

We used the DAVID web tool to perform KEGG enrichment analysis on 451 DEGs. The DEGs (227) were mapped to Gene Ontology (GO) terms and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways, and a p-value less than 0.05 was used as an enrichment screening cutoff. A total of eighteen functional clusters of the DEGs were identified (Figure 2), including 'cell cycle' (26 genes), 'pathways in cancer' (22 genes), 'oocyte meiosis' (13 genes), 'DNA replication (11 genes), 'p53 signalling pathway', 'chemical carcinogenesis', 'drug metabolism- cytochrome p450' and 'mismatch repair.

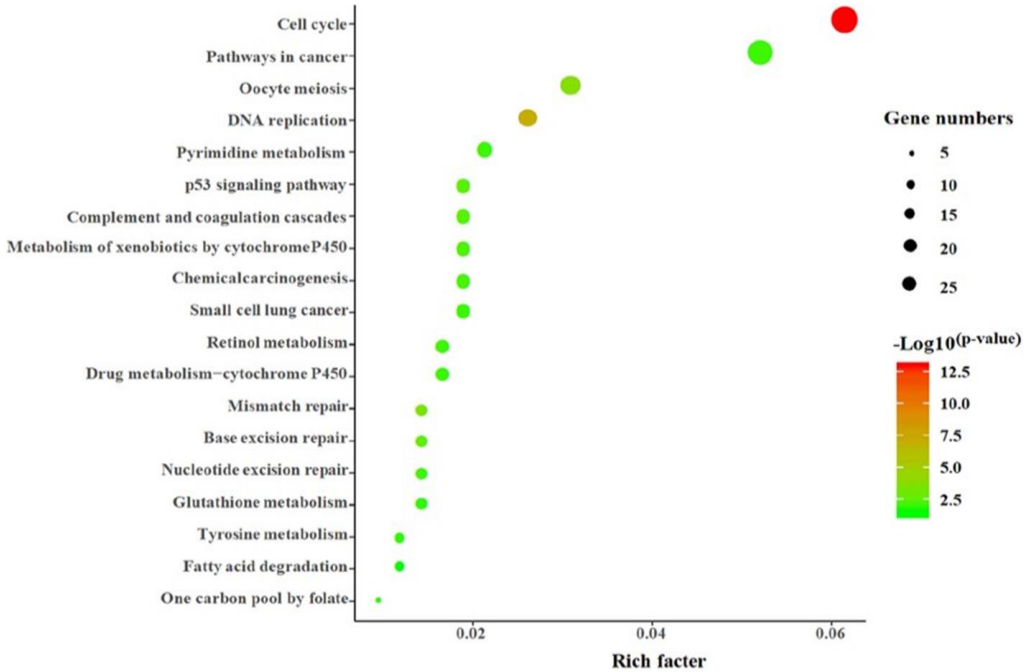

Figure 2. KEGG analysis of differentially expressed genes.

Construction of PPI networks

Furthermore, the protein-protein interaction (PPI) network of 445 DEGs was constructed using Cytoscape and the key modules were selected from the PPI network based on the MCODE analysis. The parity connected gene nodes that are removed. The remaining DEGs together constituted a complex interaction network map to analyze the connection between DEGs. The results identified 412 nodes and 3,670 edges. Among the 412 nodes, nine DEGs with the highest degree of nodes were screened based on the Cytoscape analysis (Figure 3). The results were as follows: cyclin B1 (CCN B1), proliferating cell nuclear antigen (PCNA), DNA topoisomerase II α (TOP2A), replication factor C subunit 4 (RFC4), CD K1, cyclin A2 (CCNA2), flap structure- specific endonuclease 1 (FEN 1), CD K2 and aurora kinase A (AURKA). The key modules were obtained using MCODE, with 87 hub genes with a genomic degree greater than 5. The two key modules with the highest degree were selected, and the functional and pathway enrichment of genes in these two modules was analyzed using DAVID online tools (Figure 4A and B). Module 1 consisted of 58 nodes and 1,643 edges, mainly involved in ‘oocyte meiosis, ‘cell cycle’, and ‘DNA replication. Module 2 consisted of seventeen nodes and 56 edges, which were associated with 'pyrimidine metabolism, ‘complement and coagulation cascades, and ‘chemokine signalling pathway (Table III).

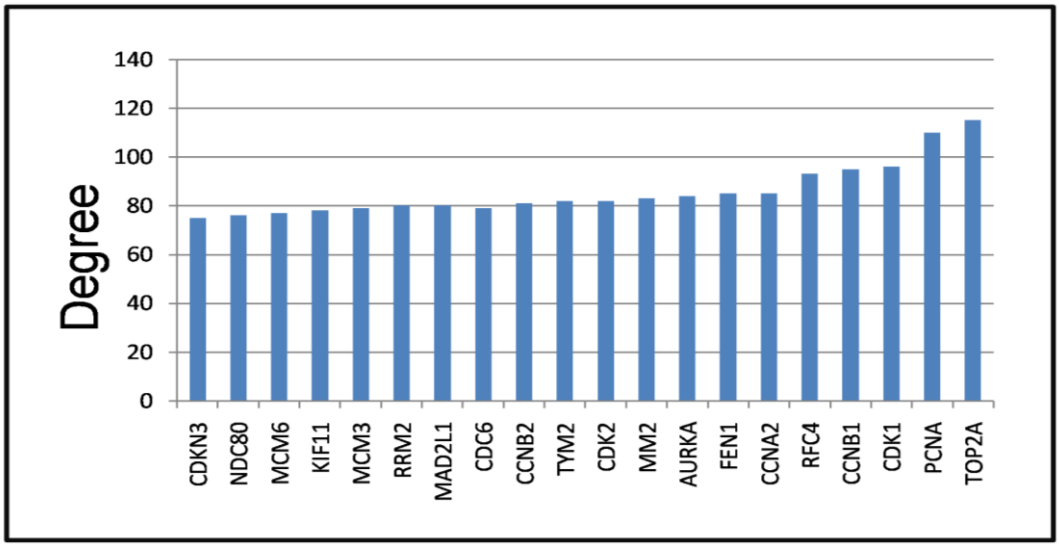

Figure 3. Top 20 hub genes in SCLC.

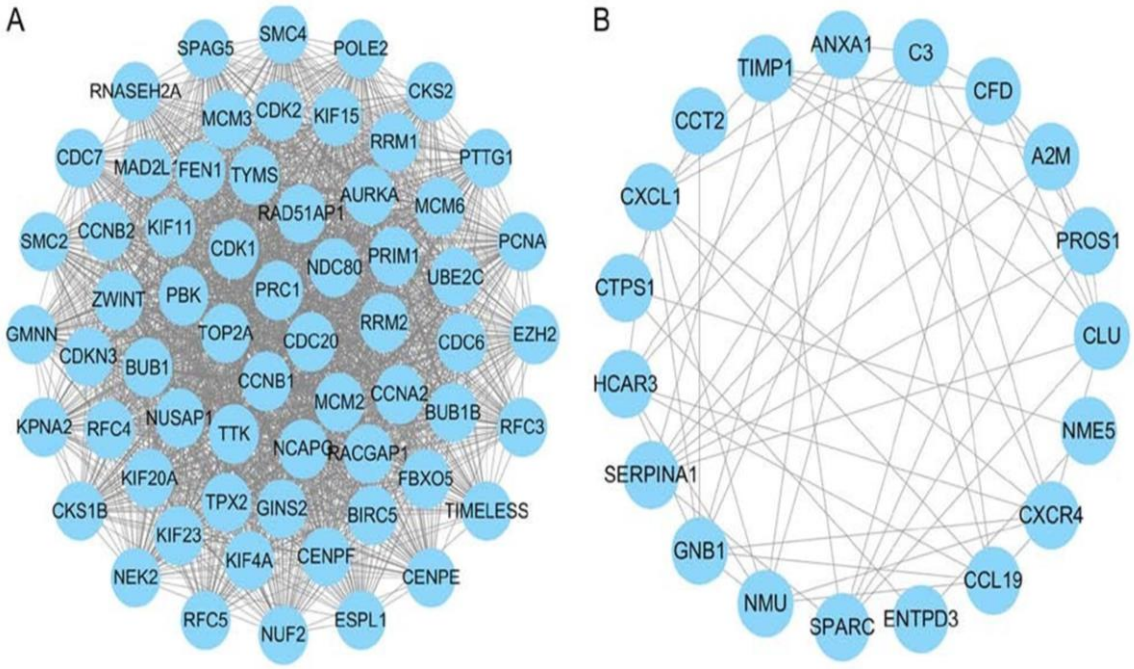

Figure 4. Two modules from the PPI interaction network analysis. (A) Module 1, (B) module 2.

Table III. KEGG analysis of module 1 and 2.

Category	Term	P-value	Count	Genes
Module 1	hsa04110: Cell cycle	$2.48x10^{-21}$	18	CDC7, CDC6, CDK1, TTK, CDC20, ESPL1, PTTG1, MCM2, CDK2, MCM6, CCNB1, MAD2L1, CCNB2, BUB1, BUB1B, CCNA2
	hsa03030: DNA replication	$6.53x10^{-16}$	11	RFC5, PRIM1, RFC3, RFC4, POLE2, PCNA, MCM2, MCM3, RNASEH2A, FEN1,
	hsa04114: Oocyte meiosis	$1.04x10^{-10}$	11	CCNB1, CDK1, MAD2L1, CCNB2, BUB1, FBXO5, AURKA, CDC20, ESPL1, PTTG1, CDK2
	hsa04914: Progesterone-mediated oocyte maturation	$4.16x10^{-6}$	7	CCNB1, CDK1, MAD2L1, CCNB2, BUB1, CCNA2, CDK2
	hsa03420: Nucleotide excision repair	$8.58x10^{-5}$	5	RFC5, RFC3, RFC4, POLE2, PCNA
	hsa03430: Mismatch repair	$1.99x10^{-4}$	4	RFC5, RFC3, RFC4, PCNA
	hsa04115: p53 signaling pathway	$3.43x10^{-4}$	5	CCNB1, CDK1, CCNB2, RRM2, CDK2
	hsa00240: Pyrimidine metabolism	$1.62x10^{-3}$	5	PRIM1, TYMS, POLE2, RRM2, RRM1
	hsa03410: Base excision repair	$1.20x10^{-2}$	3	POLE2, PCNA, FEN1
Module 2	hsa04610: Complement and coagulation cascades	$6.19x10^{-4}$	5	A2M, C3, SERPINA1, CFD, PROS1
	hsa04062: Chemokine signaling pathway	$4.55x10^{-3}$	4	CXCL1, CXCR4, GNB1, CCL19
	hsa00240: Pyrimidine metabolism	$1.50x10^{-2}$	3	NME5, CTPS1, ENTPD3

miRNA- gene regulatory network

The miRNA Walk platform identified 1,387 miRNA- gene regulatory pairs containing 552 target genes of the DEmiRNas (Figure 5). There were eighteen overlapping genes between target genes of the DEmiRNAs and DEGs. A total of eighteen overlapping genes [SOX11, fibroblast growth factor 9 (FGF9), polypyrimidine tract binding protein 2 (PTBP2), Kruppel like factor 5 (KLF5), lamin B1 (LMNB1), nucleolar protein 4 (NOL 4), collagen type IV α 1 chain (COL 4A1), HLF transcription factor(HLF), cysteine and glycine-rich protein 2 (CSRP2), RAD 21 cohesin complex component (RAD 21), cadherin EGF LAG seven- pass G- type receptor 3 (CEL SR3), PAR bZIP family member, kinesin family member 11 (KIF11), CD P- diacylglycerol synthase 1 (CD S1), erythrocyte membrane protein band 4.1 like 4B (EPB41L4B), SOX4, aldehyde dehydrogenase 1

family member A1 (ALDH1A1), ISLLI M homebox 1 (ISL1) and fibulin 1 (FBLN 1) were regulated by 28 different miRNAs (Figure 6A). The eighteen significantly up-regulated or down-regulated genes and 28 DEmiRNAs are shown in a heat- map (Figure 7A and B). Additionally, 3 target genes (RAD 21, KIF11 and MSH2) of the eighteen overlapping genes belonged to the hub genes of GSE6044 and were regulated by 5 different miRNAs (miR- 21, miR- 25, miR- 92a, miR- 181a, and miR- 101 (Figure 6B and Figure 8).

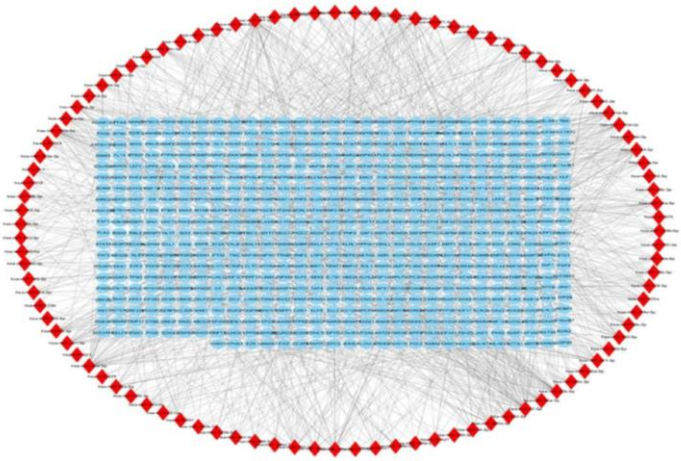

Figure 5. Protein-Protein Interaction network of miRNA-gene pairs. Diamonds denote miRNAs, and circles denote target genes predicted by miRNAs.

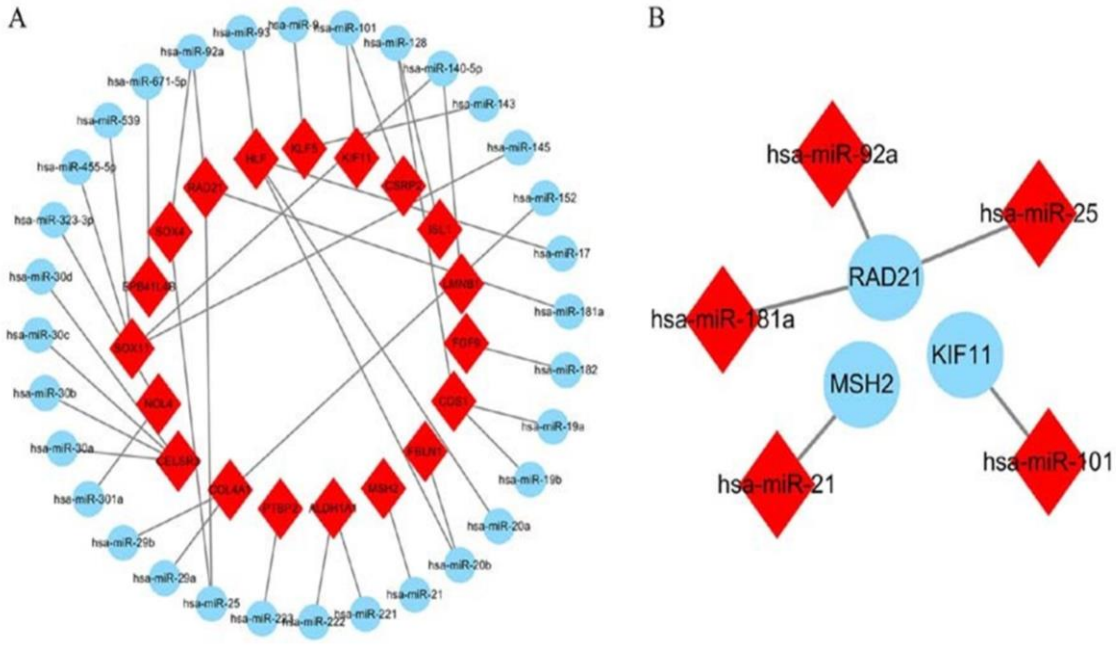

Figure 6. (A) Protein-Protein Interaction network of eighteen target genes, regulated by 28 DE-miRNAs. (B) 3 hub genes were regulated by 5 different miRNAs.

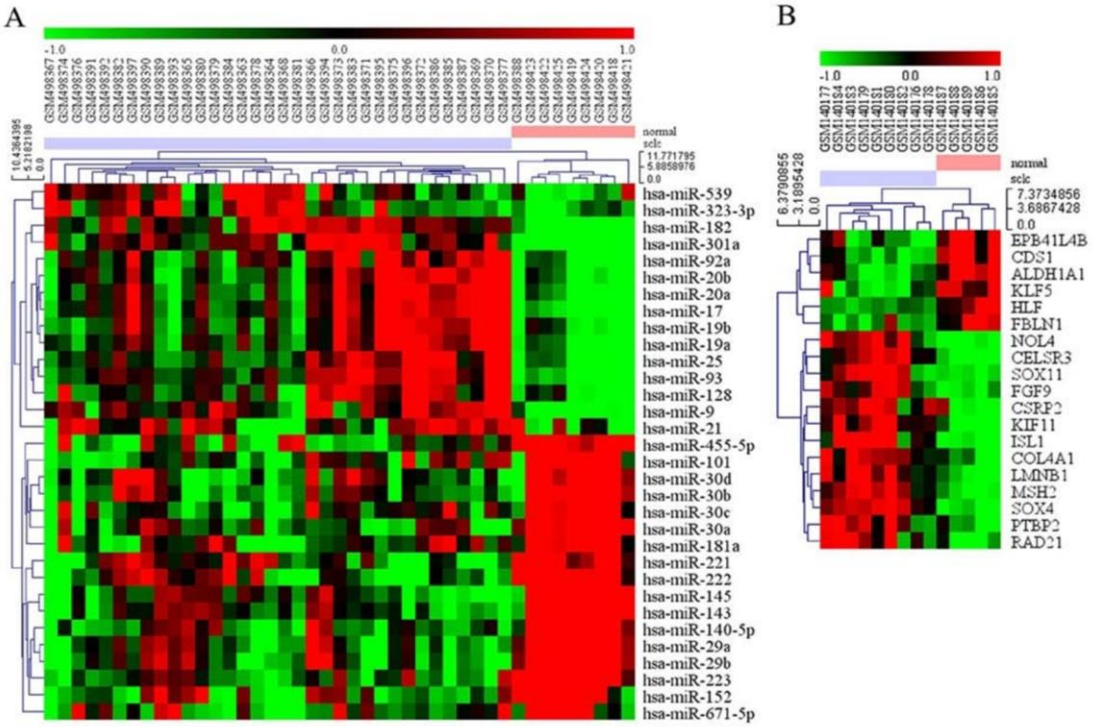

Figure 7. (A) Heat-map showing the expression of 28 DEmiRNAs. (B) Heat map showing the expression profiles of eighteen DEGs. The red and blue colors respectively represented high and low gene expression, increased expression intensity represented from green to black to red.

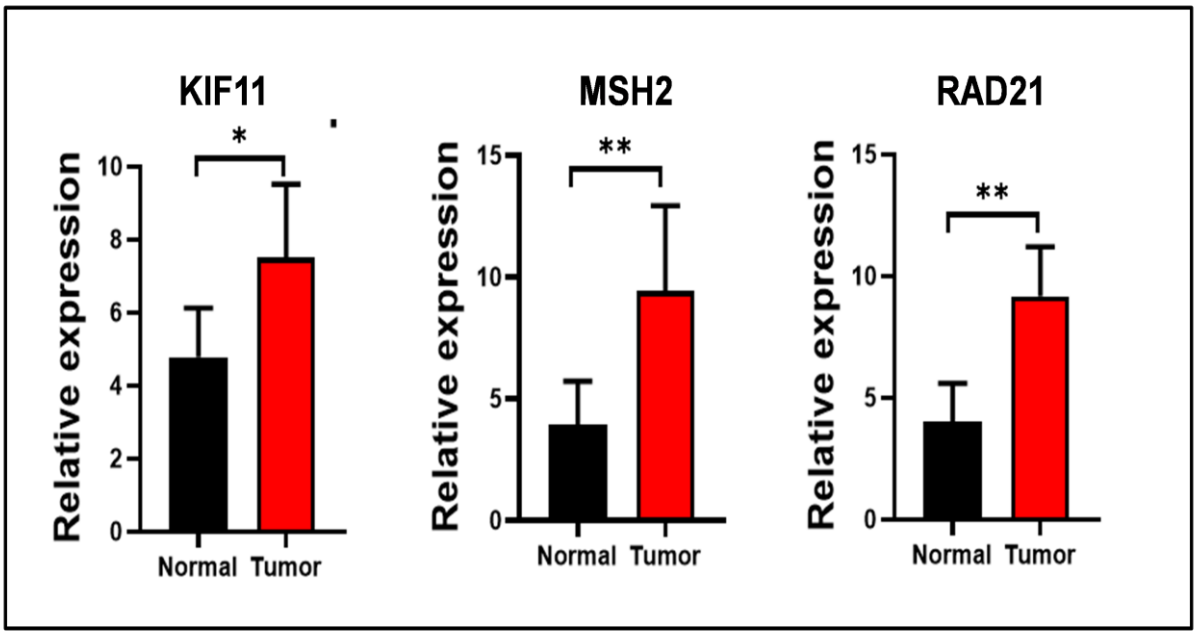

Figure 8. Expression levels of three genes are significantly different between SCLC tumor tissue and adjacent normal control lung tissues in the GSE6044 dataset.

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Small cell lung carcinoma is characterized by highly invasive and metastatic capacity. The median survival time of patients with the advance disease is only 10-15 months and the 2-year survival rate is less than 5%[15]. The high mortality rate is attributed to the fact that most patients are diagnosed with distant metastasis, which is often accompanied by a poor prognosis[16]. The pathogenesis of SCLC progression at the molecular level is not well understood. Therefore, there is an urgent need to identify potential biomarkers for the early diagnosis of SCLC. Microarray is a well-established, cost-effective, high-throughput technology, useful in studying the changes in transcription and epigenetics of SCLC genes, which is an effective approach for identifying potential biomarkers. In addition, dysregulation of various miRNAs has been shown to have critical roles in the occurrence, metastasis and recurrence of SCLC. In this study, bioinformatics tools were used to identify the DEGs and DEmiRNAs of SCLC, and the miRNA-gene regulatory network was constructed to search the molecular and pathological mechanisms of SCLC. In the current study, 445 DEGs were identified from the GSE6044 dataset. The KEGG and GO enrichment analysis of the DEGs showed that the genes enriched in many signalling pathways, such as cell cycle, p53 signalling pathway, DNA replication, and oocyte meiosis' were mostly up-regulated, but the expression levels of genes aggregated in mismatch repair, nucleotide excision repair, and 'base excision repair' were underexpressed. Previous research suggested that the aberrant expression of p53 in SCLC leads to the activation of related signalling pathways, accompanied by the activation of downregulated genes, such as MDM2, p21, PCNA and CKD1 and PCNA, which promotes tumor cell proliferation and inhibits apoptosis of cancer cells[7]. The loss or increased expression of kinases during cell mitosis leads to tumor cell proliferation and carcinogenesis[17]. Altered expression or methylation of key genes, including TFIIH core complex helicase subunit, ERCC excision repair 3, 8-oxoguanine DNA glycosylase, AGT and ATM, in classical DNA repair pathways, such as mismatch repair and nucleotide excision repair, will result in loss of the ability to repair DNA damage, leading to tumor formation or drug resistance[18,19]. In addition, other enriched functional clusters contained glutathione metabolism, complement and coagulation cascades, drug metabolism-cytochrome P450, and chemical carcinogenesis. Furthermore, ten core network nodes were screened from the PPI network, which is considered the key genes for the progression of SCLC. Recent research showed that TOP2A is overexpressed in SCLC[20]. In this study, microarray analysis identified altered miRNA expression profiles in SCLC. In the current dataset (GSE19945), 78 were upregulated and 45 were downregulated, in which two miRNAs (miR- 1290 and miR- 1) was the most significantly regulated in different types of cancer; miR-1290 inhibit MT1G and promote the progression of NSCLC[21]. Furthermore, the integration of the miRNA-gene regulatory pairs and DEGs revealed that there are eighteen over- lapping genes regulated by 28 different miRNAs. Gene Ontology (GO) enrichment analysis of GSE6044 revealed that 3 target

genes (RAD21, KIF11 and MSH2) belong to the hub genes and are regulated by 5 different miRNAs (miR-181a, miR- 101, miR- 21, miR- 92a and miR-25). Among them, three genes RAD21, KIF11 and MSH2 showed the highest degree, indicating that these 3 genes may play a crucial role in SCLC. This study revealed that the downregulation of miR-101 may lead to the increased expression of KIF11. MiR-101 was also shown to be downregulated in different types of cancer, such as lung, colon and breast cancer[22]. In the GSE6044 and GSE19945 datasets, miR-21 was upregulated in SCLC, and the higher the expression level of miR-21 was associated with the advance stage of cancer. The expression level of RAD21 is regulated by miR-181a, miR-92a and miR-25. The RAD21 gene maintains sister chromatid binding and ensures correct replication, DNA double-strand break repair and meiotic recombination[23,24]. Aberrant expression of RAD21 is shown in various cancers such as breast, lung and rectal cancer, and serves a role in tumor progression, prognosis and treatment[25–27]. Consistent with previous studies, the present results also indicated that miR-92a is overexpressed in SCLC. High expression of miR-92a enhances drug resistance and is associated with poor survival of SCLC, and is thus considered as a predictive biomarker for drug resistance and survival prognosis[28]. MiR-181a promotes macrophage-associated tumor cell metastasis by targeting KLF6 and C/EBPα [29]. MiR-25 has been shown to be associated with cell proliferation and invasion in SCLC cell lines[30].

4. CONCLUSION

In conclusion, this study analyzed gene and miRNA expression in tissue samples of SCLC patients and normal lung tissues using SCLC transcription sequencing and miRNA data from the online GEO database. The results identified differential expression of mRNAs and miRNAs in SCLC patients. Based on bioinformatics analysis, the signalling pathways of differentially expressed gene enrichment were identified. The hub genes including RAD21, KIF11 and MSH2, are regulated by miRNAs. Hence these three genes are identified as biomarkers for the diagnosis, prognosis and the prediction and detection of therapeutic response of SCLC. However, further research is required to verify the results.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The author confirms that the data supporting the findings of this research are available within the article.

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CONFLICT OF INTEREST

Authors have no conflict of interest.

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