Analysis for the mechanism between the small cell lung cancer and non-small cell lung cancer combing the miRNA and mRNA expression profiles

Weisan Zhang1, Qiang Zhang1, Mingpeng Zhang1, Yun Zhang1, Fengtan Li2 & Ping Lei1

1 Department of Geriatrics, Tianjin Geriatric Institute, Tianjin, China
2 Department of Radiology, Tianjin Medical University General Hospital, Tianjin, China

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Correspondence
Fengtan Li, Department of Radiology, Tianjin Medical University General Hospital, Tianjin 300052, China.
Tel: +86 22 27219052
Fax: +86 22 27219052
Email: 2969495607@qq.com

Ping Lei, Department of Geriatrics, Tianjin Geriatric Institute, Tianjin Medical University General Hospital, Tianjin 300052, China.
Tel: +86 22 27219219
Fax: +86 22 60363578
Email: leiping1974@163.com

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Abstract
Background: We investigated the relationship between small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) based on micro ribonucleic acid (miRNA) and messenger (m)RNA expression profiles.

Methods: Utilizing the differentially expressed mRNAs and the targeting miRNAs, the mRNA-miRNA network for the two cancers was constructed. By integrating the miRNA expression profile, drug, and drug targets, miRNA-drug target-drug networks were established and the mechanisms in drug therapy efficacy were compared between SCLC and NSCLC.

Results: Drug targets of different expressed miRNAs of SCLC are mainly located in the organelle, act in the electron carrier activity, and consist of the synapse; while drug targets of NSCLC are the membrane-enclosed lumen, mainly distributed in the extracellular region and synapse, and function in the binding. Drug targets of miRNA expressed commonly in the two cancers are involved in the reproduction multi-organism process. In SCLC, the miR-16 in the miRNA-drug target-drug network is significant and follows the result of the mRNA-miRNA network. The pigmentation and rhythmic process of SCLC is different from NSCLC, while the process of cellular component biogenesis and cellular component organization are important for the occurrence of NSCLC. miR-16 in the miRNA-mRNA-drug network of SCLC is significant and we acquired 11 potential drugs, such as dexamethasone and budesonide. The miR-124 for NSCLC is important in the network and 17 potential drugs were screened, including dexamethasone and budesonide.

Conclusions: These findings suggest that miR-16 and miR-124 might be novel diagnostic and prognostics markers for SCLC and NSCLC, respectively.

Introduction
Lung cancer is the second most common cancer1 and one of the few cancers to have a clear cause in many cases. Researchers are attempting to find screening tests that may help to diagnose lung cancer earlier, such as sputum cytology,2 imaging tests,3 and tissue samples (biopsy).4 Lung cancer is divided into two main types, known as small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC).5 SCLC accounts for approximately 20% of lung cancers,6,7 while NSCLC accounts for 80%, including three subtypes: adenocarcinoma, squamous cell, and large cell carcinoma.8,9 Each subtype relates to the specific type of cell affected and are grouped together because they behave in a similar way.10,11 Finding a distinction between SCLC and NSCLC when viewing a tumor under a microscope is important for proper treatment. Surgery is the treatment of choice for the early stage of NSCLC.12 There are differences between NSCLC and SCLC in the evolution process, such as in the differentiation and prognosis of the tumor, and SCLC can also develop into NSCLC.13 It is necessary to distinguish the difference in occurrence mechanisms of SCLC and NSCLC in order to provide a more effective and individualized treatment of lung cancer.14

Increased research has shown that more than half of human genes are targets of evolutionarily conserved micro ribonucleic acid (miRNA) regulation.15 miRNAs are the non-coding RNAs that down-regulate gene expression and play an...
important role in cellular processes, such as stress responses, differentiation, and apoptosis.\(^\text{19}\) Moreover, miRNAs regulate the amount of genes that become diseased, and further induce the occurrence of implicated diseases including cardiovascular\(^\text{17}\) and neurological diseases.\(^\text{28}\) In lung cancer research, a series of miRNAs are found (let-7g, miR-21, miR-150, miR-146a, let-7d, let-7e, let-7f, miR-125a, miR-183, miR-20a, miR-210, miR-218, miR-22 and miR-423). Specifically, miR-21 is a miRNA expression signature of human solid tumours that defines cancer gene targets.\(^\text{19}\) MiR-125a,\(^\text{20}\) miR-150,\(^\text{21}\) and miR-146a\(^\text{22}\) are the unique miRNA molecular profiles in lung cancer diagnosis and prognosis. Notably, miR-146a\(^\text{23}\) inhibits cell growth and migration, and induces apoptosis in NSCLC cells. Capodanno et al.\(^\text{24}\) have shown that let-7g reduced expression of the let-7 miRNAs in human lung cancers in association with shortened postoperative survival and miR-21 is an epidermal growth factor receptor (EGFR)-regulated anti-apoptotic factor in NSCLC in never-smokers. miR-183,\(^\text{25}\) miR-21, miR-210, miR-218, miR-22, and miR-423 are the microRNA 133B, which target prosurvival molecules MCL-1 and BCL2L2 in lung cancer. miR-20a\(^\text{26}\) counterbalances between RB inactivation and miR-17–92 overexpression in reactive oxygen species and DNA damage induction in lung cancers. Recently, major observation of miRNAs suggested that miRNAs could determine the efficacy of drugs and gave rise to the field of miRNA pharmacogenomics.\(^\text{27}\) miRNAs are essential for tissue identity and cell-specific regulation and changes in them may directly cause disease or have a secondary effect on other cell regulatory changes.\(^\text{28}\) miRNAs regulate many genes involved in pharmacogenomics and diverse miRNAs will affect pharmacogenomic related genes differently, which cause various consequences to the effect of the drug. Some studies have proven that the variations in miRNA patterns in similar diseases lead to differences in gene expression\(^\text{29,30}\) and further affect the drug function. Increased miRNA levels may result in down-regulated genes with products promoting drug efficacy, and lowered miRNA levels may cause the up-regulated genes encoding proteins to inhibit drug function.\(^\text{31}\)

Based on the regulation relationship between miRNA and mRNA in the biological system, it is important to understand the principle of these molecules in the biological signal and reaction mechanism of energy metabolism in disease and other special physiological states. In this study, we combined miRNA and mRNA expression profile data to research the different mechanisms of SCLC and NSCLC. It is known that the pathology of a disease is connected with different expression profiles and disease specific biomarkers could supply potential targets for clinical therapy.\(^\text{32}\) Here, we analyze the function enrichment of mRNAs regulated by different expressed miRNAs for SCLC and NSCLC. Furthermore, we constructed two kinds of networks: the mRNA-miRNA network and the mRNA-mRNA-drug network for SCLC and NSCLC, and extracted the key miRNAs as the biomarkers for SCLC and NSCLC, which are the hub nodes in the network.

**Material and method**

**Messenger ribonucleic acid (mRNA) expression profile**

The mRNA expression profile GSE40275, published on 25 August 2012 from the Gene Expression Omnibus (GEO, http://www.ncbi.nlm.nih.gov/geo/) focused on the differences in gene expression profiles among SCLC, NSCLC, and normal lung samples regarding the expression of gene encoding for proteins with G protein-coupled receptor activity. We grouped the adenocarcinoma, squamous cell and large cell carcinomas into NSCLC. In our research, there were 84 samples, including 25 SCLC, 16 NSCLC, and 43 normal lung RNA samples (human) and the gene expression analysis was performed using Affymetrix microarrays. We downloaded the data and analyzed the mechanisms of SCLC and NSCLC based on a global view. Using a t-test for differential expression analysis, we compared the gene expression profiles of SCLC, NSCLC, and normal tissues. We acquired the significantly different expression genes using a P-value of less than 0.05 as the signature. Based on the GPL15947, we translated the probe number of genes into gene symbols. Consequently, we obtained 9682 different expression genes of NSCLC and 7381 different expression genes of SCLC, with 4600 genes shared by NSCLC and SCLC. We downloaded the miRNA from miRBase (Release 20: June 2013, http://www.mirbase.org/), and selected the miRNAs that targeted the different expressed genes of SCLC and NSCLC.

**Micro (mi)RNA expression profiling**

We also downloaded the miRNA profiles of NSCLC and SCLC, GSE27486 and GSE27435, respectively, from GEO. In GSE27486, fifth generation Exiqon locked nucleic acid miRCURY LNA microarrays were applied to profile the expression of miRNAs in the whole blood of 22 NSCLC cases and 23 controls. GSE8824 contained four miRNA expression profiles of SCLC cell lines versus the normal lung, and four SCLC cell lines (H69, HTB-172, HTB-173 and HTB-184) were compared to a mixed RNA sample derived from six normal lung tissue samples. Using a t-test for the miRNA profile, we selected 442 NSCLC and 239 SCLC significantly different expressed miRNAs, with 69 miRNAs found in both NSCLC and SCLC.

**mRNA – miRNA network of small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC)**

We downloaded the mRNA-miRNA associations from miRBase and extracted the miRNAs that targeted the...
different expressed mRNAs of SCLC and NSCLC, respectively. Using Cytoscape software, we constructed mRNA–miRNA networks for SCLC and NSCLC. We then analyzed the topological properties of the networks and abstracted the hub miRNAs that had the highest degree. Subsequently, we queried the target genes of the miRNAs and took functional annotation from the KEGG pathway and three aspects of GO (biological process, molecular function and cellular components).

Biological function comparison of drug targets regulated by miRNAs for SCLC and NSCLC

We downloaded the approved targets of miRNA from TarBase, miRecords, miRTarBase and selected the target genes of the different expressed miRNAs for SCLC and NSCLC. We obtained 2143 miRNA–mRNA regulated pairs of SCLC, including 124 miRNAs and 1388 mRNAs. There were 1651 miRNA–mRNA regulated pairs of NSCLC, including 89 miRNAs and 1240 mRNAs. We acquired the drugs and drug targets from the DrugBank and STICH. Subsequently, we screened the drug and drug targets potentially related to SCLC and NSCLC according to the target genes of miRNA from the integrated mRNA-drug pairs. Through the mRNA, 637 mRNA-drug pairs of SCLC were obtained, including 63 mRNA and 319 drugs, and 323 pairs of NSCLC, including 44 mRNAs and 210 drugs. Finally, we enriched the miRNA regulated drug targets to study the mechanism difference between SCLC and NSCLC in the drug metabolism pathway and biological processes.

miRNA–drug target–drug network of SCLC and NSCLC

According to the relationship among miRNAs, drug targets, and drugs, highly relational miRNA–drug pairs were obtained. Furthermore, combining the miRNA-target regulation relationships and drug–drug target pairs, we constructed a miRNA-drug target–drug network for SCLC and NSCLC. Based on network topological features, we selected the hub node that was the highest degree in the network and screened its regulation relationship.

Results

mRNA–miRNA network of SCLC and NSCLC

We obtained 4562 mRNA–miRNA associations of NSCLC consisting of 229 miRNA and 1393 mRNA. We analyzed the network and acquired the key node, concluding that miR-335-5p targets 232 mRNA, and owns the highest degree and betweenness. After functional annotation for the mRNA of miR-335-5p, we found that 49 genes were involved in the developmental process, including the glycoprotein, organic acid, hormone, and isoprenoid metabolic processes. Twenty-one genes are enriched in the Golgi apparatus, 19 genes are located in the Golgi membrane, 42 genes in the plasma membrane, 22 genes in the Golgi apparatus, and 108 genes in the membrane (Fig 1a). There are four genes enriched in the structural constituent of the eye lens.

The miRNA–mRNA network of SCLC was established based on 1000 miRNA–mRNA pairs, including 176 miRNA and 264 mRNA. In this network we concluded that miR-16-5p is the key node that has the highest betweenness and degree. MiR-16-5p targets 38 mRNA and we annotated the target gene of miRNA from the GO biological process, cellular components, molecular function, and KEGG pathway.

The enrichment of drug targets regulated by miRNA

To analyze the drug metabolic mechanism of SCLC and NSCLC, we selected drug targets that are targeted by miRNAs and enriched the drug target genes into the GO and KEGG pathways. The drug targets of SCLC and NSCLC were 63 and 44, respectively.

In molecular function, both of the targets for SCLC and NSCLC play a pivotal role in molecular transducer and catalytic activity. The target genes for SCLC and NSCLC function in the binding. In the cellular component, the targets of the two diseases are located in the extracellular region and organelle. The target genes of SCLC consist of the synapse, while the genes of NSCLC are membrane-enclosed lumen. In the biological process, both of the target genes of miRNA for SCLC and NSCLC function in the reproductive multi-organism process (Table 1). However, the tiniest differences in biological process will induce the disease. In SCLC, the pigmentation and rhythmic processes are different from NSCLC, while the process of cellular component biogenesis and organization are significant for the occurrence of NSCLC.

miRNA–mRNA–drug relationship for the NSCLC and SCLC

After data integration, we obtained 4104 miRNA–mRNA pairs, including 290 miRNAs and 2487 target genes and 7297 miRNA–drug relationships constituting 813 mRNA and 683 drugs. Combining the miRNA–mRNA and mRNA–drug pairs, the number of drug targets shared by miRNA and drugs was 63 and 44 for SCLC and NSCLC, respectively (Fig 2).

Furthermore, we acquired miRNA–drug pairs for SCLC and NSCLC according to the drug targets regulated by miRNA and obtained 940 miRNA–drug target-drug
relationships for SCLC and 538 relationships for NSCLC (Table 1). In SCLC, 59 miRNAs share the mRNAs with drugs, and in NSCLC, 38 miRNAs share the mRNA with drugs. We ascertained that miR-211 acts on all of the drug targets and is related to 10 drugs in SCLC; in NSCLC, half of the mRNA targeted by the miRNA are drug targets – miR-26b, miR-433 and miR-101 (Table 2).

**miRNA-drug target-drug network**

We merged the miRNA-mRNA and mRNA-drug networks and acquired the miRNA-target-drug network of SCLC and NSCLC (Fig 3), which show that miRNAs play a core role in drug metabolism. In the SCLC network (Fig 3a), the highest degree node is miR-16, which targets 192 mRNAs. We extracted the sub-network of miR-16 (Fig 3b) and concluded that miR-16 targets five drug proteins: prostaglandin-endoperoxide synthase 2 (PTGS2), F2, serine/threonine-

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**Table 1** The biological process enrichment of drug targets regulated by miRNA for SCLC and NSCLC

| Biological adhesion | Biological adhesion |
|---------------------|---------------------|
| Biological regulation | Biological regulation |
| Cellular process | Cellular component biogenesis |
| Death | Cellular component organization |
| Developmental process | Cellular process |
| Immune system process | Death |
| Localization | Developmental process |
| Locomotion | Immune system process |
| Metabolic process | Localization |
| Multicellular organismal process | Locomotion |
| Multi-organism process | Metabolic process |
| Pigmentation | Multicellular organismal process |
| Reproduction | Multi-organism process |
| Reproductive process | Reproduction |
| Response to stimulus | Reproductive process |
| Rhythmic process | Response to stimulus |

miRNA, micro ribonucleic acid; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

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Figure 1 The enrichment of the targeted genes of miR-335-5p and miR-16-5p. (a) The cellular components for the targeted genes of miR-335-5p. (b) The molecular function for the targeted genes of miR-16-5p. (c) The biological process for the targeted genes of miR-16-5p. (d) The cellular component for the targeted genes of miR-16-5p.

Figure 2 The drug targets regulated by micro ribonucleic acid (miRNA) for small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). There are 1240 miRNA targets for NSCLC, 1388 miRNA targets for SCLC and 813 drug targets.
protein kinase (PLK1), vascular endothelial growth factor (VEGF)A and CHUK, which are targeted by 47 drugs. We annotated the five genes into GO (molecular function, cell component and biological process). There are four genes (PTGS2, VEGFA, F2, CHUK) involved in the multicellular organismal process and three genes (PTGS2, VEGFA, CHUK) involved in the developmental process. F2 is located in the extracellular region, CHUK in the organelle, PLK1 in the membrane-enclosed lumen, and VEGFA is located in the extracellular region, the membrane-enclosed lumen. In molecular function: F2 take part in catalytic, binding, and molecular transducer activity; CHUK acts in catalytic activity and binding; and PLK1 functions in catalytic activity. There are three genes involved in the pathways in cancer: PTGS2, VEGFA, and CHUK. VEGFA and CHUK are involved in pancreatic cancer and PTGS2 and CHUK take part in SCLC. More specifically, F2 acts in the pathway of neuroactive ligand-receptor interaction, complement and coagulation cascades, and in the regulation of actin cytoskeleton. CHUK is involved in the signalling pathway, acute myeloid leukemia, and SCLC. PLK1 takes part in the cell cycle, oocyte meiosis, and progesterone-mediated oocyte maturation. PTGS2 is essential for the arachidonic acid metabolism, VEGF signalling pathway, and pathways in cancer, including SCLC. VEGFA plays a pivotal role in Cytokine-cytokine receptor interaction, the mammalian target of rapamycin (mTOR) signalling pathway, focal adhesion, renal cell carcinoma, and pathways in cancer, such as pancreatic and bladder cancers. miR-16 are frequently deleted or down-regulated in squamous cell carcinomas and adenocarcinomas of the lung.
Overexpression of miRNA induces cell cycle arrest in G1-G0 and is likely to distinguish the tumorigenesis between SCLC and NSCLC.

In the miRNA-drug target-drug network of NSCLC (Fig 3c), miR-124 is the highest degree, and 263 mRNAs are targeted by miR-124. From the sub-network of miR-124 (Fig 3d), we obtained that miR-16 targets five drug target genes (CYP1B1, NR3C1, NR3C2, PRKD1 and SEC11A), which are then targeted by 118 drugs. All five genes are the components of organelle and cell parts, take part in metabolic and cellular processes, and function in the binding. Four genes (CYP1B1, PRKD1, NR3C1 and NR3C2) are in the process of biological regulation. CYP1B1 (cytochrome P450, family 1, subfamily B, polypeptide 1) encodes a member of the cytochrome P450 superfamily of enzymes. The cytochrome P450 proteins are monooxygenases, which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. The enzyme encoded by CYP1B1 localizes to the endoplasmic reticulum and metabolizes procarcinogens, such as polycyclic aromatic hydrocarbons. PRKD1 (protein kinase D1) is a serine/threonine kinase that regulates a variety of cellular functions, including membrane receptor signalling and protection from oxidative stress at the mitochondria. NR3C1 (nuclear receptor subfamily 3, group C, member 1) encodes the glucocorticoid receptor, which can function both as a transcription factor that binds to glucocorticoid response elements in the promoters of glucocorticoid responsive genes to activate their transcription.

Figure 3 Micro ribonucleic acid (miRNA)-target-drug network. Red represents miRNA, blue is messenger ribonucleic acid (mRNA) and yellow is the drug. (a) miRNA-target-drug network of small cell lung cancer (SCLC). (b) The sub-network of miRNA-target-drug network of SCLC, which consists of miR-16, its target gene, and the drug. (c) miRNA-target-drug network of non-small cell lung cancer (NSCLC). (d) The sub-network of miRNA-target-drug network of NSCLC, which consists of miR-124, its target gene, and the drug.
and as a regulator of other transcription factors. NR3C2 (nuclear receptor subfamily 3, group C, member 2) encodes the mineralocorticoid receptor, which mediates aldosterone actions on salt and water balance within restricted target cells. The protein functions as a ligand-dependent transcription factor that binds to mineralocorticoid response elements in order to transactivate target genes. NR3C1 and NR3C2 specifically act in the multicellular organismal process.

In cellular components, the five drug targets are the components of organelle and cell parts. SEC11A, CYP1B1, and PRKD1 act at catalytic activity. SEC11A is the SEC11 homolog A (S. cerevisiae), encodes a member of the peptidase S26B family. The encoded protein is an 18kDa subunit of the signal peptidase complex and has been linked to cell migration and invasion, gastric cancer and lymph node metastasis. Specifically, NR3C1 and NR3C2 play a role in transcription regulator and molecular transducer activity. CYP1B1 is involved in steroid hormone biosynthesis, tryptophan metabolism, and metabolism of xenobiotics by cytochrome P450. NR3C1 is involved in neuroactive ligand-receptor interaction, and NR3C2 acts in the pathway of aldosterone-regulated sodium reabsorption.

**Discussion**

In this study, we determined from GO annotation that miR-335-5p plays a role in structural molecule activity and the developmental process. Moreover, the target genes of miR-335-5p are involved in glycosphingolipid biosynthesis in the KEGG pathway. Gong et al. reported that the overexpression of miR-335 in SBC-5 cells significantly reduced cell migration, invasion, proliferation, and further inhibits SCLC bone metastases via insulin-like growth factor-I receptor (IGF-IR) and receptor activator of nuclear factor kappa-B ligand (RANKL) pathways. In NSCLC, miR-335 is highly expressed, thus, miR-335 could be a significant marker to distinguish NSCLC from SCLC. MiR-16-5p, the hub node in the miRNA-mRNA network in SCLC, belongs to miR-16 and the altered expression of miR-16 has been observed in cancers, including lung, prostate, and brain cancers. MiR-16 is clustered within a 0.5 kbp region in chromosome 13 in humans which is deleted or down-regulated in more than half of B-cell chronic lymphocytic leukemias. This difference in expression levels of miRNA-16 could be utilized to distinguish healthy and cancerous tissues and to determine clinical prognosis. The loss of mir-16 observed in a large percentage of cells indicates that the change occurred early in cancer development, which could be a target for therapeutic intervention. In molecular function, there are 26 target genes of miR-16-5p playing a role in catalytic activity. Twenty genes are enriched in purine nucleoside binding and nucleoside binding (Fig 1b). In the pathway, the target genes of miR-16-5p involve the tight junction. There are 25 target genes of miR-16-5p mainly enriched in the metabolic process, specifically, the cellular nitrogen compound, ribonucleotide, and purine nucleotide biosynthetic processes (Fig 1c). In the cellular component, the target genes of miR-16-5p take part in the envelope, especially the mitochondrial and organelle envelopes. There are 13 genes involved in the mitochondrion and 24 involved in the intracellular membrane-bounded organelle (Fig 1d). By comparison, miR-335-5p plays a role in the developmental process, while miR-16-5p is mainly involved in the metabolic process, envelope, and catalytic activity. Yan et al.’s research has identified that miR-335 could be the prognostic biomarker to assess the recurrence risk and prognosis of gastric cancer patients. Ke et al. reported that the down regulation of miR-16 promotes growth and motility by targeting hepatoma-derived growth factor (HDGF) in NSCLC cells, while miR-16 is overexpressed in SCLC. Therefore, we infer that miR-16 is the potential marker to distinguish between SCLC and NSCLC. Moreover, according to the different biological process and molecular functions of SCLC and NSCLC, miR-16-5p and miR-335-5p could be potential biomarkers.

The same miRNA may target multiple genes that are relevant for the function of one particular drug. Multiple miRNAs are often deregulated in the same disease tissue and drug resistance may be the result of the combined actions of several miRNAs working on different genes. Because one miRNA may target and modify the expression of several genes in the same pathway, it is important to develop miRNA-based drugs. Based on the miRNA-mRNA-drug network of SCLC and NSCLC, we could screen miR-16 and miR-124, respectively, as potential biomarkers. We classified the related drugs of miR-16 and miR-124 based on the anatomical therapeutic chemical (ATC) code system (Fig 4) and concluded that both of the miRNA-related drugs acting in the antineoplastic and immunomodulating agents account for a large percentage.

For miR-16, we acquired 47 related drugs and 11 drugs have been approved: argatroban, budesonide, celecoxib, dexamethasone, diclofenac, gefitinib, ibuprofen, imatinib, rosiglitazone, simvastatin, and thalidomide. Two drugs – dexamethasone and budesonide – belong to the respiratory system (Fig 4a) and are potential treatment drugs in SCLC. For example, dexamethasone is a glucocorticoid agonist, and unbound dexamethasone crosses cell membranes and binds with high affinity to specific cytoplasmic glucocorticoid receptors. This complex binds to DNA elements (glucocorticoid response elements), which results in a modification of transcription and, hence, protein synthesis, in order to achieve inhibition of leukocyte infiltration at the site of inflammation, interference in the function of mediators of inflammatory response, suppression of humoral immune responses, and reduction in edema or scar tissue. The anti-inflammatory actions of dexamethasone are thought...
to involve phospholipase A2 inhibitory proteins and lipocortins, which control the biosynthesis of potent mediators of inflammation, such as prostaglandins and leukotrienes. The ability of the PTGS2 promoter to bind GR$\alpha$ in response to dexamethasone diminished during incubation. miR-16 activates the PTGS2 and the PTGS2 is then targeted in the process of drug therapy. Thus, miR-16 is a potential biomarker in the process of SCLC treatment.

We obtained 118 drugs related to miR-124, 17 of which have been approved: budesonide, ciclesonide, clozapine, daunorubicin, dexamethasone, docetaxel, doxorubicin, eplerenone, estradiol, estrogens, imatinib, omeprazole, paclitaxel, progesterone, tamoxifen, testosterone, and triamcinolone. After ATC classifying (Fig 4b), there are five drugs belonging to the respiratory system: dexamethasone, budesonide, triamcinolone, ciclesonide, and aminophylline. In disease treatment, drugs interact with proteins and miRNA acts on these targets. Dexamethasone is a glucocorticoid agonist used in the treatment of respiratory diseases and endocrine, hematologic, and neoplastic diseases. Unbound dexamethasone crosses cell membranes and binds with high affinity to specific cytoplasmic glucocorticoid receptors. This complex binds to DNA elements (glucocorticoid response elements), which results in a modification of transcription and, hence, protein synthesis, in order to achieve inhibition of leukocyte infiltration at the site of inflammation, interference in the function of mediators of inflammatory response, suppression of humoral immune responses, and reduction in edema or scar tissue. The anti-inflammatory actions of dexamethasone are thought to involve phospholipase A2 inhibitory proteins and lipocortins, which control the biosynthesis of potent mediators of inflammation, such as prostaglandins and leukotrienes. Dexamethasone targets NR3C1 in the treatment of disease and is regulated by miR-124. Changes to miR-124 will affect the function of NR3C1 and further affect the treatment efficiency of drugs.

**Conclusion**

Recently, some studies have reported that different expressed miRNAs are involved in different lung cancer types and are key components in gene regulatory networks. It is useful to explore their functional roles in regulatory processes in order...
to understand the different mechanisms between SCLC and NSCLC. There have been a number of studies on miRNAs, including biological experiments and computational approaches, to explore their functions and mechanisms. In order to learn the occurrence mechanism of the two lung cancers, we studied the functions of miRNAs in the cancers according to the regulation relationships between miRNAs and mRNAs. Utilizing the mRNA expression profile, we constructed a mRNA-miRNA network and predicted two key miRNAs that could be potential biomarkers for SCLC and NSCLC (miR-16-5p and miR-335-5p, respectively). miRNA should be tested with further experiments. Furthermore, according to the miRNA expression profile and drug targets, we built the miRNA-drug target -drug network, and acquired two biomarkers to distinguish SCLC and NSCLC, miR-16 and miR-124, respectively. According to the network, we obtained a series of drugs, which can be potential drugs for lung cancer therapy. However, one challenge as these drugs approach clinical use is testing for interactions between the novel miRNA drugs and traditional drugs already in the market. Based on the two kinds of networks, we concluded that miR-16 is the potential biomarker of SCLC, and miR-133 and miR-124 are the possible biomarkers of NSCLC. Future studies are planned to continue testing.

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Disclosure
No authors report any conflict of interest.

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**Supporting information**

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:

Table S1: The miRNA-drug target-drug relationships for SCLC and NSCLC.

Table S2: The percentage of miRNA targets drug targets and the number of drugs that share the same mRNAs with the given miRNA for SCLC and NSCLC.