MicroRNAs and Lung Cancer: A Review Focused on Targeted Genes

Yao-Hui Wang¹,²,³, Zhi-Ruo Zhu¹,²,³, De Tong¹,²,³, Rui Zhou¹,²,³, Kui Xiao¹,²,³* and Ling Peng⁴*.

¹Department of Respiratory and Critical Care Medicine, The Second Xiangya Hospital of Central South University, Changsha, Hunan, China; ²Research Unit of Respiratory Disease, Central South University, Changsha, Hunan, China; ³The Respiratory Disease Diagnosis and Treatment Center of Hunan Province, Changsha, Hunan, China; ⁴Department of Respiratory Disease, Zhejiang Provincial People’s Hospital, Hangzhou, Zhejiang, China.

Abstract

Lung cancer is the leading cause of cancer morbidity and mortality. Surgery, chemotherapy and radiotherapy techniques have been developed over many years, and anti-angiogenic therapy, molecular targeted therapy and immune-checkpoint inhibitors have become increasingly effective for treating lung cancer. However, the overall disease-free and survival rates of lung cancer remain quite low. MicroRNAs are small, non-coding RNAs that consist of an average of 22 nucleotide molecules. MicroRNAs play an important role in the development, progression, metastasis, diagnosis and prognosis of lung cancer. This review summarizes the recent publications abnormally expressed miRNAs and the abnormal expression of their target genes in the biological process of lung cancer. This review aims to shed light on the recent advances in this field and to provide perspectives for future directions.

Keywords: MicroRNAs; Lung cancer; Pathogenesis; Diagnosis; Therapy.

Introduction

Histologically, lung cancer can be divided into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC is more common than SCLC, accounting for about 80% of all cases. NSCLC includes squamous cell carcinoma (SCC), adenocarcinoma, and large cell carcinoma, among which, adenocarcinoma and SCC are the most common subtypes. MicroRNAs (miRNAs) are small non-coding RNAs composed of an average of 22 nucleotides and are the most commonly studied non-coding RNAs in lung cancer. miRNAs mainly bind to the 3′ untranslated region of a target mRNA, which degrades target mRNA or blocks protein translation to regulate gene expression. miRNAs are involved in the regulation of the cell cycle, metastasis, angiogenesis, metabolism and apoptosis, and play an important role in the occurrence and development of tumors.

miRNAs in the development and progression of lung cancer

The occurrence and development of cancer is complex. The biological processes of cancer mainly include the occurrence of cancer, growth and metabolism, tumor microenvironment, neovascularization, tumor invasion and metastasis. A full understanding of the regulatory mechanisms and modes of action of miRNA in the occurrence and development of lung cancer may provide new strategies for the diagnosis and treatment of lung cancer. In the following sections, we will focus on the role of miRNAs in these processes.

miRNAs in the occurrence of lung cancer

The role of miRNAs in the occurrence of lung cancer manifests as targeting both oncogenes and tumor suppressor genes. The causes of lung cancer are complex and are mainly related to abnormal genes. These abnormalities usually occur in areas where genes are not stable. Studies have found that a transcriptional hyper-conserved region gene is located in an unstable genomic region associated with cancer. This super-conserved region consists of a genomic sequence family of more than 200 base pairs (bp) in length. Most transcriptional hyper-conserved region...
genes are not translated into proteins and act as oncogenes to promote carcinogenesis by inhibiting miRNAs. There are also some miRNAs involved in the development of lung cancer. Oncogenic miRNA-411 promotes lung cancer by directly targeting the inhibitory genes SPRY4 and TXNIP.

**Table 1. MicroRNAs involved in the cell cycle and apoptosis**

| miRNAs    | Targets/pathway      | Tumor suppressor/oncogene | Lung cancer type | Ref          |
|-----------|----------------------|---------------------------|------------------|--------------|
| miR485-5p | IGF2BP2              | suppressor                | NSCLC           | Huang et al.17|
| miR183    | MTA1                 | suppressor                | NSCLC           | Yang et al.18|
| miR335    | Tra2β                | suppressor                | NSCLC           | Liu et al.19 |
| miR188    | MAP3K3               | suppressor                | NSCLC           | Zhao et al.20|
| miR186    | SIRT6                | suppressor                | NSCLC           | Ruan et al.21|
| miR93-5p  | PTEN and RB1         | oncogene                  | NSCLC           | Yang et al.22|
| miR4326   | APC2                 | oncogene                  | NSCLC/SCLC      | Xu et al.23  |
| miR339    | Skp2                 | suppressor                | NSCLC/SCLC      | Ren et al.24 |
| miR520b   | HDAC4                | suppressor                | NSCLC/SCLC      | Jin et al.25 |
| miR628-3p | HSP90                | suppressor                | NSCLC/SCLC      | Pan et al.26 |
| let7a     | cyclin D1            | suppressor                | Human Lung adenocarcinoma | Zhao et al.27|
| miR505    | MAP3K3               | suppressor                | NSCLC           | Tang et al.28|
| miR135a   | IGF1                 | suppressor                | NSCLC           | Zhou et al.16|

miRNAs involved in tumor growth and metabolism

miRNAs involved in the cell cycle and apoptosis

The cell cycle is the basis of cell proliferation, which, in addition to apoptosis, are two important processes of tumor growth and are closely related to miRNAs. Of note, miR21 inhibits apoptosis by inhibiting the PI3K/Akt/NF-κB signaling pathway in NSCLC in vitro and in vivo. Also, miR19b enhances proliferation and apoptosis resistance through the epidermal growth factor receptor (EGFR) signaling pathway in NSCLC by targeting PP2A and BIM. Overexpression of miR143 significantly reduces cell proliferation and promotes apoptosis, and miR335-5p inhibits cell proliferation by targeting CPNE1 in NSCLC. Other miRNAs involved in cell cycle and apoptosis are shown in Table 1.16-28

miRNAs involved in the metabolism of lung cancer

Altered metabolism is an important feature in the development of cancer. Various miRNAs can directly or indirectly participate in various metabolic processes of lung cancer cells, including glucose metabolism, amino acid metabolism and lipid metabolism, which provide the rapidly multiplying cells with much needed energy. At present, the research on the metabolism of miRNAs in lung cancer is mostly studied by glucose metabolism. High glucose promotes cell proliferation, migration and invasion in NSCLCs.15 By reviewing articles on miRNAs and lung cancer metabolism, it has been found that miRNAs involved in cancer metabolism mainly play a role in the regulation of a series of biological enzymes involved in the metabolic processes. The Warburg effect (aerobic glycolysis) is a common feature of cancer cells, which facilitates tumor cell proliferation and progression with elevated glucose uptake and lactate production. Lactate dehydrogenase A (LDHA), one of the subunits of lactate dehydrogenase, participates in the final step of the aerobic glycolysis process by catalyzing pyruvate into lactate. In fact, a recent study found that miR200c can inhibit the proliferation and migration of NSCLC cells by down-regulating LDHA. Downregulation of miR33b promotes NSCLC cell growth by reprogramming glucose metabolism. In NSCLC cells, down-regulated miR214 inhibits cell proliferation and glycolysis by reducing the expression of HK2 and PDKM2 via the PTEN/Akt/mTOR pathway. Pyruvate dehydrogenase kinase 4 (PDK4) and pyruvate dehydrogenase (PDH) are important biological enzymes in sugar metabolism and fatty acid synthesis, respectively. It has been reported...
that the overexpression of miR-182 can regulate PDH through the miR182-PDK4 axis. PDK4 is activated and lipogenesis promotes lung cancer cell proliferation and tumor growth. Overexpression of miR182 and PDK4 knockdown significantly promotes triglyceride levels, suggesting that miR182 and PDK4 affect lipogenesis in lung cancer cells. Another miRNA, miR198, inhibits the proliferation of lung adenocarcinoma cells in vitro and in vivo by directly targeting SHMT1, which leads to enhanced apoptosis and leads to cell cycle arrest in lung adenocarcinoma.

### miRNAs involved in the formation of the tumor microenvironment and angiogenesis

miRNAs involved in the tumor microenvironment of lung cancer

Disordered miRNAs can affect cancer proliferation, angiogenesis, tumor metastasis, etc., by regulating the tumor microenvironment.

miRNAs involved in tumor angiogenesis

Neovascularization ensures that the required nutrients and oxygen are brought to the tumor tissue and is a backup force in the progression of the tumor. Many studies have demonstrated that miRNAs have a regulatory role in tumor angiogenesis. Vascular endothelial growth factor (VEGF) is more important in this process because it directly stimulates vascular endothelial cells to promote neovascularization and increase microvascular permeability. It has also been found that miR143/145 in lung adenocarcinoma significantly promotes tumor angiogenesis by stimulating the proliferation of endothelial cells, mainly through the targeting of Camk1d (an inhibitory kinase) by miR145. There is also a lung cancer-derived exosome miR23a that increases angiogenesis and vascular permeability by targeting prolyl hydroxylase and tight junction protein ZO-1 under hypoxic conditions. Studies have shown that in NSCLC, miR1 can reduce VEGF-induced mouse lung endothelial cell proliferation. The miRNA also reduces de novo DNA synthesis by targeting the thrombopoietin receptor in lung endothelial cells and by activating extracellular signal-regulated protein kinase 1/2 in human umbilical vein endothelial cells to inhibit tumor growth and angiogenesis. MiR135a inhibits tumor angiogenesis by inhibiting IGFl by decreasing the expression of angiogenesis-related factors VEGF, bFGF and IL8 in A549 cells. Furthermore, miR204 may attenuate angiogenesis in lung adenocarcinoma via the JAK2-STAT3 pathway. These studies have shown that miRNAs play various roles in tumor angiogenesis. Other miRNAs that affect tumorigenesis through the tumor microenvironment are shown in Table 2.

### miRNAs involved in tumor invasion and metastasis

Invasion and metastasis are complicated processes that are both important causes of the poor prognosis of cancer. A large number of studies have found that miRNA expression profiles are closely related to the invasion and metastasis of lung cancer. Exosomal-mediated miR193a-3p, miR210-3p and miR5100 metastasis can promote lung cancer cell invasion by activating STAT3 signaling-induced EMT. Overexpressed miR302b-3p inhibits the proliferation, migration and invasion of NSCLC cells by the direct targeting of GCNT3. In NSCLC, miR409 inhibits the growth, proliferation and migration of cancer cells by directly targeting SPH1. MiR-520a3p inhibits proliferation, migration and invasion of NSCLC cells by the PI3K/AKT/mTOR signaling pathway. A summary of the miRNAs involved in tumor invasion and metastasis are shown in Table 3.

### The role of miRNAs in the diagnosis of lung cancer

The lack of effective means of early diagnosis is the main cause of the high mortality rate of lung cancer. As such, miRNAs are often dysregulated in lung cancer and form a specific expression spectrum, which is conducive to the diagnosis of lung cancer. In a meta-analysis, the authors claimed that they could determine if a person has lung cancer based on whether 11 miRNAs, including miR210, miR21, miR155, were contained in a sputum specimen (1,009 NSCLC patients and 1,006 controls). It has also been found that the combination of miR205-5p and miR210-3p may be useful in the diagnosis of early stage lung cancer. Relevant studies found that by analyzing the serum of lung cancer patients that the expression of miR661, miR441 and miR181B-5 was significantly increased compared with healthy controls. These results indicated that miRNAs can be used as serum markers for the diagnosis of lung cancer. Overall, the efficacy of a combined imaging approach for the early diagnosis of lung cancer was significantly increased.

### The role of miRNAs in the treatment of lung cancer

Chemotherapy, radiotherapy, targeted therapy and ICI therapy are...
MicroRNAs and lung cancer

Explor. Res. Hypothesis Med

Wang Y.-H. et al: MicroRNAs and lung cancer

Chemotherapy

Platinum drugs, such as cisplatin and carboplatin, are commonly used in lung cancer chemotherapy regimens; however, the resistance of NSCLC cells to platinum-based drugs is a common cause of poor efficacy. Therefore, miRNAs are associated with chemotherapy sensitivity and drug resistance. The sensitivity of cisplatin in miR155 overexpressing NSCLC cell lines is reduced. Furthermore, in NSCLC, the up-regulation of miR128-3p may over-activate Wnt/β-catenin and TGFβ signaling and confer resistance to chemotherapy-resistant metastasis. Some studies have also found that miR96-reduced cisplatin-induced NSCLC cell apoptosis is caused by down-regulating SAMD9 expression. Other miRNAs that are associated with chemosensitivity or resistance to lung cancer are shown in Table 4.

Radiotherapy

Radiotherapy is a treatment that uses radioactive rays to destroy cancer cells and is suitable for selected NSCLC and SCLC patients. However, the efficacy of radiotherapy is limited and some patients are prone to relapse, which may be due to radiation resistance in their cancer cells. Studies have shown that cell radiosensitivity is associated with apoptosis as well as cell cycle and DNA damage. Therefore, it is particularly important to find the cause and markers that affect radiotherapy resistance. Studies have shown that, in vitro, miR155 reduces the radiotherapy sensitivity of lung cancer by inhibiting FOXO3A and TP53INP1. By contrast, inhibiting the expression of miR155 can improve the radiotherapy effect. Shin et al. studied the human lung adenocarcinoma cell line A549 and found that the expression level

| miRNA   | targets                      | Tumor suppressor/oncogene | Lung cancer type | Ref          |
|---------|------------------------------|----------------------------|-----------------|--------------|
| miR210  | LOXL4                        | oncogene                   | lung adenocarcinoma | Xie et al. 54 |
| miR342-3p | AGR2                        | suppressor                 | NSCLC           | Xue et al. 55 |
| miR3666 | BPTF                         | suppressor                 | NSCLC           | Pan et al. 56 |
| miR146-5p | claudin12                   | oncogene                   | NSCLC           | Sun et al. 57 |
| miR33a  | CAND1                        | suppressor                 | NSCLC           | Kang et al. 58 |
| miR889  | KLF9                         | oncogene                   | NSCLC           | Han et al. 59 |
| miR93-5p | PTEN and RB1                | oncogene                   | NSCLC           | Yang et al. 62 |
| miR103  | PDCD10                       | suppressor                 | NSCLC           | Yang et al. 60 |
| miR223-5p | E2F8                        | suppressor                 | NSCLC           | Dou et al. 61 |
| miR449a | HMGB1                        | suppressor                 | NSCLC           | Wu et al. 62 |
| miR373  | BRF2                         | suppressor                 | NSCLC           | Wang et al. 63 |
| miR214  | JAK1                         | suppressor                 | NSCLC           | Chen et al. 64 |
| miR101  | ZEB1                         | suppressor                 | NSCLC           | Han et al. 65 |
| miR204  | PCNA1                        | suppressor                 | NSCLC           | Li et al. 66 |
| miR758  | HMGB3                        | suppressor                 | NSCLC           | Zhou et al. 67 |
| miR497-5p | SOX5                        | suppressor                 | NSCLC           | Li et al. 68 |
| miR1246 | GSK3β                        | oncogene                   | NSCLC           | Yang et al. 69 |
| miR362  | Sema3A                       | oncogene                   | NSCLC           | Luo et al. 70 |
| miR128-3p | Drosha and Dicer           | oncogene                   | NSCLC           | Frixia et al. 71 |
| miR320a-3p | PI3K/Akt pathway           | suppressor                 | NSCLC           | Zhao et al. 72 |
| miR875-5p | SATB2                        | oncogene                   | NSCLC           | Wang et al. 73 |
| miR26a-5p | ITGB8                      | oncogene                   | NSCLC, SCLC    | Song et al. 74 |
| miR320a | p100                         | suppressor                 | NSCLC, SCLC    | Xing et al. 75 |
| miR145-3p | PDK1                        | suppressor                 | NSCLC           | Chen et al. 76 |
| miR212  | USP9X                        | suppressor                 | NSCLC           | Chen et al. 77 |
| miR24-3p | SOX7                         | oncogene                   | NSCLC, SCLC    | Yan et al. 78 |
| miR150  | SIRT2/JMJD2A pathway         | oncogene                   | NSCLC           | Jiang et al. 79 |
of 8 miRNAs changed after 20 Gy and 40 Gy-exposure, while that of 10 miRNAs changed only after 40 Gy-exposure. Studies have found that the down-regulation of miR18a expression can increase the sensitivity of NSCLC cells to radiotherapy.\textsuperscript{100} Other miRNAs that associated with sensitivity or resistance to lung cancer radiotherapy are shown in Table 5.\textsuperscript{101–108}

**Molecular targeted therapy**

Many studies have reported the role of various miRNA expressions in targeted therapies. Tyrosine kinase inhibitor (TKI) is a small molecule that targets the intracellular tyrosine signaling pathway. EGFR is a glycoprotein receptor consisting of 1,186 amino acid residues with a molecular weight of 170kD. After activation, EGFR can lead to intracellular tyrosine kinase activation and phosphorylation through copolymerization to activate downstream RAS-Raf-MAPK, PI3K-Akt, and JAK/STAT pathways. This process can thereby mediate tumor cell proliferation, angiogenesis, and apoptosis inhibition. Interestingly, TKIs such as gefitinib and erlotinib are often used to treat EGFR-sensitive mutant lung cancer patients. The miRNA, miR483-3p, reverses EMT and inhibits migration, invasion and metastasis of gefitinib-resistant lung cancer cells.\textsuperscript{109} This indicates that the overexpression of Mir483-3p can effectively improve the sensitivity of gafitinib-resistant lung cancer cells to gafitinib. Other miRNAs that are associated with molecular targeted therapy for lung cancer are shown in Table 6.\textsuperscript{109–114}

**Immunotherapy**

There are programmed death-1 (PD-1) proteins in the membrane of T-cells, which, if bound with the programmed death-ligand 1 (PD-L1) on tumor cells, can be redirected to kill these tumor cells. While this theory exists, little research has been published in this field. The up-regulation of miR140 in NSCLC directly inhibits the PD-L1 and the PD-L1/cyclin E pathway to inhibit cell pro-

**Table 4. MicroRNAs associated with chemosensitivity or resistance to lung cancer**

| miRNA   | Up/down | Target/pathway | Medicine | Ref.      |
|---------|---------|----------------|----------|-----------|
| miR9    | UP      | eIF5A2         | Cisplatin| Cai et al.\textsuperscript{85} |
| miR539  | UP      | DCLK1          | cisplatin| Deng et al.\textsuperscript{88} |
| miR202  | UP      | Ras/MAPK Pathway| cisplatin| Sun et al.\textsuperscript{90} |
| miR155  | UP      | miR155/TP53 feedback loop| Cisplatin| Van Roosbroeck et al.\textsuperscript{92} |
| miR106b-5p | UP    | PKD2           | Cisplatin| Yu et al.\textsuperscript{94} |
| miR140  | UP      | SIRT1/ROS/JNK  | Cisplatin| Lin et al.\textsuperscript{96} |

**Chemo-sensitive**

**Chemo-resistant**

| miRNA   | Up/down | Target/pathway | Medicine | Ref.      |
|---------|---------|----------------|----------|-----------|
| miR373  | Up      | TIMP2          |          | Guo et al.\textsuperscript{101} |
| miR18a-5p | Up    | ATM and HIF1α  |          | Chen et al.\textsuperscript{103} |
| miR200a | Up      | HGF/c-Met pathway|          | Jiang and Du et al.\textsuperscript{104,105} |
| miR144-5p | Up    | ATF2           |          | Song et al.\textsuperscript{107} |
| miR99a  | Up      | mTOR           |          | Yin et al.\textsuperscript{108} |

**Radio-sensitive**

| miRNA   | Up/down | Target/pathway | Ref.      |
|---------|---------|----------------|-----------|
| miR198  | down    | HGF/c-MET pathway| Zhu et al.\textsuperscript{102} |
| miR21   | UP      | HIF1α          | Jiang et al.\textsuperscript{104} |
| miR1323 | down    | PRKDC          | Li et al.\textsuperscript{106} |

**Radio-resistant**

**Table 5. MicroRNAs associated with sensitivity or resistance to lung cancer radiotherapy**

| miRNA   | Up/down | Target/pathway | Ref.      |
|---------|---------|----------------|-----------|
| miR373  | Up      | TIMP2          |          | Guo et al.\textsuperscript{101} |
| miR18a-5p | Up    | ATM and HIF1α  |          | Chen et al.\textsuperscript{103} |
| miR200a | Up      | HGF/c-Met pathway|          | Jiang and Du et al.\textsuperscript{104,105} |
| miR144-5p | Up    | ATF2           |          | Song et al.\textsuperscript{107} |
| miR99a  | Up      | mTOR           |          | Yin et al.\textsuperscript{108} |

**Radio-sensitive**

| miRNA   | Up/down | Target/pathway | Ref.      |
|---------|---------|----------------|-----------|
| miR198  | down    | HGF/c-MET pathway| Zhu et al.\textsuperscript{102} |
| miR21   | UP      | HIF1α          | Jiang et al.\textsuperscript{104} |
| miR1323 | down    | PRKDC          | Li et al.\textsuperscript{106} |
The role of miRNAs in the prognosis of lung cancer

In a study of the prognostic role of circulating miRNAs in early NSCLC, five miRNAs (miR26a-5p, miR126-3p, miR130b-3p, miR205-5p and miR21-5p) were found to be significantly associated with disease-free survival (DFS) in SCC after surgical operation. Furthermore, four miRNAs (miR130b-3p, miR26a-5p, miR126-3p and miR205-5p) were found to be significantly correlated with overall survival. In adenocarcinoma, miR222-3p, miR22-3p and miR93-5p were significantly associated with DFS, and other miRNAs are thought to be involved in the prognosis of lung cancer. The 5-year survival rate of patients with low expression of miR455-3p in SCLC is significantly shorter than that of patients with high expression of miR455-3p. High expression of miR421 is associated with positive lymph node metastasis and advanced TNM staging, and has been shown to be an independent prognostic factor for NSCLC. Serum miR150 predicts the prognosis of early (stage I–II) NSCLC and can promote tumor cell proliferation by targeting the tumor suppressor gene SRCIN1.

Future directions

Studies have shown that the abnormal expression of miRNAs can be detected in many types of tumors and that miRNAs play an important role in tumorigenesis. A large number of studies have reported on the relationship between miRNAs and lung cancer and have shown that miRNAs may bring certain benefits to the early diagnosis, treatment and prognosis of lung cancer. In fact, miRNAs may be a target for drug development, and can directly participate in the proliferation, apoptosis, metabolism, invasion and metastasis of lung cancer cells or indirectly enhance the sensitivity of chemotherapy, radiotherapy, targeted therapy or immunotherapy. However, due to the large number of miRNAs and the complexity and diverse regulatory pathways of lung cancers, there are still many questions to be answered.

As of now, experts have extensively investigated the relationship between microRNAs and lung cancer, but are still looking for miRNAs that can be stably expressed in the human body and that can be helpful in the diagnosis and treatment of tumors. We expect more work to participate in studying the relationship between microRNAs and lung cancer, which is expected to bring benefits to human health in the future.

Conclusions

Although there are a large number of studies on the relationship between miRNAs and lung cancer, miRNAs have not been applied to the clinical diagnosis and treatment of lung cancer. There may be a number of issues that need to be considered before a miRNA can be used in a clinical setting. For example, the safety of miRNA in the application process must be evaluated, in addition to whether a miRNA has high sensitivity and specificity for different individuals. Furthermore, it must be examined whether a miRNA is suitable for all patients and can be continuously and stably expressed in vivo. Nevertheless, the role of miRNAs in lung cancer research has attracted many attentions and will continue to provide insights into this disease as more mechanisms are revealed.

Acknowledgments

None.

Funding

This work was supported by the Excellent-Surpass-Climb Disciplines Project of The Second Xiangya Hospital of Central South University; the Scientific Research Project of Hunan Provincial Health Commission, (No. 202103020704) and the National Key Clinical Specialty Construction Projects of China.

Conflict of interest

The authors declare that there is no conflict of interest.

Author contributions

Conceptualization (YHW, DT), methodology (DT, ZRZ), writing of the original draft (YHW, DT, KX), writing, review and editing of the manuscript (YHW, KX, LP, ZRZ). All authors have made an intellectual contribution to the manuscript and approved the submission.

Table 6. MicroRNAs associated with molecular targeted therapy for lung cancer

| miRNA    | Up/down | Target/pathway          | Medicine | Ref.     |
|----------|---------|-------------------------|----------|----------|
| miR135a  | UP      | RAC1                    | Gefitinib| Zhang et al.  
| miR200c  | UP      | PI3K/Akt pathway        | Gefitinib| Zhou et al.  
| miR181a  | UP      | GAS7                    | Gefitinib| Ping et al.  
| miR873   | UP      | GLI1                    | Gefitinib| Jin et al.   
| miR138   | Down    | HOXA4                   | Gefitinib| Tang et al.  
| miR483-3p| UP      | integrin β3/FAK/Erk pathway | Gefitinib| Yue et al.    |
of microRNA in tumor angiogenesis and clinical implications. Mol Cancer 2018;17(1):22. doi:10.1186/s12943-018-0766-4.

[38] Dimitrova N, Gocheva V, Bhtakar A, Resnick R, Jong RM, Miller KM, et al. Stromal Expression of mir-143-145 Promotes Neangiogenesis in Lung Cancer Development. Clin Cancer Res 2016;22(6):188–201. doi:10.1158/1078-0432.CCR-15-0584.

[39] Hsu VL, Hung JY, Chang WA, Lin YS, Pan YC, Tsai PH, et al. Hypoxic lung cancer-secreted exosomal miR-23a increased angiogenesis and vascular permeability by targeting prolyl hydroxylase and tight junction protein ZO-1. Oncogene 2017;36(34):4929–4942. doi:10.1038/onc.2017.105.

[40] Korde A, Jin L, Zhang JG, Ramaswamy A, Hu B, Kolahian S, et al. MicroRNA-105 promotes epithelial-mesenchymal transition of nonsmall lung cancer cells through upregulating Mcl-1. J Cell Biochem 2019;120(4):5880–5888. doi:10.1002/jcb.27873.

[41] Li P W, Wang Q, Wang H. MicroRNA-204 Inhibits the Proliferation, migration, and invasion by targeting SOX5 in non-small-cell lung cancer. Mol Carcinog 2018;699:94–101. doi:10.1158/0005-620X.JCO.2018.26(4):519–528. doi:10.3727/000562018X15213089759999.

[42] Liu X, Cao L, Zhang Y, Lian H, Sun Z, Cui Y. MicroRNA-1246 inhibits cell carcinoma proliferation, migration, and invasion by targeting lysyl oxidase-like 4. J Cell Physiol 2019;234(8):14050–14057. doi:10.1002/jcp.28093.

[43] Xu X, Fei X, Hou W, Zhang Y, Liu L, Hu R. miR-342-3p suppresses cell proliferation and migration by targeting AGR2 in non-small cell lung cancer. Cancer Lett 2018;412:170–178. doi:10.1016/j.canlet.2017.10.024.

[44] Pan L, Tang Z, Pan L, Tang R. MicroRNA-3666 inhibits lung cancer cell proliferation, migration, and invasiveness by targeting BPTF. Biochem Cell Biol 2019;7(9):415–422. doi:10.1139/bcb-2018-0301.

[45] Sun X, Cui S, Fu X, Liu C, Wang Z, Liu Y. MicroRNA-146p promotes proliferation, migration and invasion in lung cancer cells by targeting claudin-12. Cancer Biomark 2019;25(1):89–99. doi:10.3233/cbmr-182374.

[46] Kang M, Li Y, Zhao Y, He S, Shi J. miR-33a inhibits cell proliferation and invasion by targeting CAND1 in lung cancer. Clin Transl Oncol 2018;20(4):457–466. doi:10.1007/s12094-017-1730-2.

[47] Han X, Tang Y, Dai Y, Hu S, Zhou J, Liu X, et al. MiR-889 promotes cell growth in human non-small cell lung cancer by regulating KLF9. Gene 2019;699:94–101. doi:10.1016/j.gene.2019.02.077.

[48] Yang D, Wang J, Ji JS, Xu QY. miR-103 Functions as a Tumor Suppressor by Directly Targeting Programmed Cell Death 10 in NSCLC. Oncol Res 2018;26(4):519–528. doi:10.3727/000562018X152198894056.

[49] Wu D, Liu J, Chen J, He H, Ma H, Lu X. miR-449a Suppresses Tumor Growth, Migration, and Invasion in Non-Small Cell Lung Cancer by Targeting a HMGB1-Mediated NF-κB Signaling Pathway. Oncol Res 2019;27(2):225–237. doi:10.3727/000562018X15213089759999.

[50] Wang L, Qu J, Zhou L, Liao F, Wang J. MicroRNA-373 Inhibits Cell Proliferation and Invasion Via Targeting BRF2 in Human Non-Small Cell Lung Cancer AS49 Cell Line. Cancer Res Treat 2018;50(3):936–949. doi:10.4143/crt.2017.302.

[51] Chen X, Du J, Jiang R, Li L. MicroRNA-214 inhibits the proliferation and invasion of lung carcinoma cells by targeting JAK1. Am J Transl Res 2018;10(4):1146–1171.

[52] Han L, Chen W, Xia Y, Song Y, Zhao Z, Cheng H, et al. MiR-101 inhibits the proliferation and metastasis of lung cancer by targeting zinc finger E-box binding homeobox 1. Am J Transl Res 2018;10(4):1172–1183.

[53] Li P, Wang W, Wang H. MicroRNA-204 inhibits the proliferation, migration and invasion of human lung cancer cells by targeting PCNA-1 and inhibits tumor growth in vivo. Int J Mol Med 2019;43(3):1149–1156. doi:10.3892/ijmm.2018.4044.

[54] Zhou GH, Lu YY, Xie JL, Gao ZK, Wu XB, Yao WS, et al. Overexpression of miR-758 inhibited proliferation, migration, invasion, and promoted apoptosis of non-small cell lung cancer cells by negatively regulating HMGB1. Biosci Rep 2019;39(1):BSR20180855. doi:10.1042/bsr20180855.

[55] Li G, Wang K, Wang J, Qin S, Sun X, Ren H. miR-497-5p inhibits tumor cell growth and invasion by targeting SOX5 in non-small-cell lung cancer. J Cell Biochem 2019;120(6):10587–10595. doi:10.1002/jcb.28345.

[56] Yang F, Kong X, Huan D, Liu L, Li X, Zhou Y. MicroRNA-1246 Promotes Metastasis and Invasion of A549 cells by Targeting GSK3β-Mediated Wnt/β-Catenin Pathway. Cancer Res Treat 2019;51(4):1420–1429. doi:10.4143/crt.2018.638.

[57] Luo D, Zhang Z, Zhang L, Ji YL, Cui J, Shi WP, et al. Aberrant Expression of miR-362 Promotes Lung Cancer Metastasis through Downregulation of Sema3A. J Immunol Res 2018;2018:687097. doi:10.1155/2018/687097.

[58] Frixia T, Sacconi A, Cioce M, Roscilli G, Ferrara FF, Aurisicchio L, et al. MicroRNA-128-3p-mediated depletion of Drosha promotes lung cancer cell migration. Carcinogenesis 2018;39(2):293–304. doi:10.1093/carcin/bgw134.

[59] Zhao W, Sun Q, Yu Z, Mao S, Jin Y, Li J, et al. MicroRNA-320a-3p/ELF3 axis regulates cell metastasis and invasion in non-small cell lung cancer via PI3K/Akt pathway. Gene 2018;670:31–37. doi:10.1016/j.gene.2018.05.100.

[60] Wang J, Lu Y, Ding H, Gu T, Gong C, Sun J, et al. The miR-875-p inhibits SATB2 to promote the invasion of lung cancer cells. Gene
MicroRNAs and lung cancer

Wang Y.-H. et al.: MicroRNAs and lung cancer

[84] Chen GM, Zheng AJ, Cai J, Han P, Ji HB, Wang LL. microRNA-145-3p confers chemoresistance-associated metastasis in NSCLC cells. Nat Rev Cancer 2018;18(6):885–895. doi: 10.1038/s41585-018-02652.

[85] Zhou GH, Yang WH, Sun B. Clinical impact of serum miR-661 in diagnosis and prognosis of non-small cell lung cancer. Eur Rev Med Pharmacol Sci 2017;21(24):5696–5701. doi: 10.26355/eurrev_201712_14015.

[86] Wang SY, Li Y, Jiang YS, Li RZ. Investigation of serum miR-411 as a diagnosis and prognosis biomarker for non-small cell lung cancer. Eur Rev Med Pharmacol Sci 2017;21(18):4092–4097.

[87] Li J, Zhan Y, Feng J, Luo J, Fan S. miR-24-3p promotes cell migration and proliferation in lung cancer by targeting SOX7. J Cell Biochem 2018;119(5):3989–3998. doi: 10.1002/jcb.26553.

[88] Jiang K, Shen M, Chen Y, Xu W. miR-150 promotes the proliferation and migration of non-small cell lung cancer cells by regulating the SIRT2/MDM2A signaling pathway. Oncol Rep 2018;40(2):943–951. doi: 10.3892/or.2018.6487.

[89] Zhang X, Wang Q, Zhang S. MicroRNAs in spumum specimen as non-invasive biomarkers for the diagnosis of nonsmall cell lung cancer: An updated meta-analysis. Medicine (Baltimore) 2019;98(6):e14337. doi:10.1097/MD.0000000000014337.

[90] Leng G, Wang Y, Jiang F. A Direct Plasma miRNA Assay for Early Detection and Histological Classification of Lung Cancer. Transl Oncol 2018;11(4):883–889. doi:10.1016/j.tranon.2018.05.001.

[91] Zhou GH, Yang WH, Sun B. Clinical impact of serum miR-661 in diagnosis and prognosis of non-small cell lung cancer. Eur Rev Med Pharmacol Sci 2017;21(24):5696–5701. doi: 10.26355/eurrev_201712_14015.

[92] Wang SY, Li Y, Jiang YS, Li RZ. Investigation of serum miR-411 as a diagnosis and prognosis biomarker for non-small cell lung cancer. Eur Rev Med Pharmacol Sci 2017;21(18):4092–4097.

[93] Lu J, Zhan Y, Feng J, Luo J, Fan S. MicroRNAs associated with therapy of non-small cell lung cancer. Int J Biol Sci 2018;14(4):390–397. doi: 10.7150/ijbs.22243.

[94] Cai J, Fang L, Huang Y, Li R, Xu X, Hu Z, et al. Publisher Correction: Simultaneous overactivation of Wnt/β-catenin and TGFβ signaling by mir-128-3p confers chemoresistance-associated metastasis in NSCLC. Nat Commun 2018;9:16196. doi:10.1038/ncomms16196.

[95] Wu L, Pu X, Wang Q, Cao J, Xu F, Li L, et al. miR-96 induces cisplatin chemoresistance in non-small cell lung cancer cells by downregulating SAMD9. Oncol Lett 2016;11(2):945–952. doi: 10.3892/ol.2015.3712.

[96] Zheng Q, Zheng B, Sun L, Yan Q, Zhang Y, Zhang Z, et al. MicroRNA-130b targets PTEN to induce resistance to cisplatin in lung cancer cells by activating Wnt/β-catenin pathway. Cell Biochem Funct 2018;36(4):194–202. doi: 10.1007/s12285-018-9805-0.

[97] Deng H, Qian Qian G, Jing T, Alimin Y. miR-539 enhances chemosensitivity to cisplatin in non-small cell lung cancer by targeting DCLK1. Biomed Pharmacother 2018;107:102–1081. doi: 10.1016/j.biopha.2018.07.024.

[98] Liu HN, Qie P, Yang G, Song YB. miR-181b inhibits chemoresistance in cisplatin-resistant H464 small cell lung cancer cells by targeting Bcl-2. Arch Med Sci 2018;14(4):745–751. doi: 10.5114/ams.2018.73131.

[99] Sun W, Ping W, Tian Y, Zou W, Li J, Yu Y. miR-202 Enhances the Antitumor Effect of Cisplatin on Non-Small Cell Lung Cancer by Targeting the Ras/MAPK Pathway. Cell Physiol Biochem 2018;51(5):2160–2171. doi:10.1159/000495835.

[100] Wang W, Zhu C, Yu Y, Qian W, Zheng M. Negative Regulation of PTEN by MicroRNA-221 and Its Association with Drug Resistance and Cellular Senescence in Lung Cancer Cells. Biomed Res Int 2020;2018;7909850. doi:10.1155/2018/7909850.

[101] Van Roosbroeck K, Fanini F, Setoyama T, Ivan C, Rodriguez-Aguayo C, Fuentes-Mattie et al. Combining Anti-MiR-155 with Chemotherapy for the Treatment of Lung Cancers. Clin Cancer Res 2017;23(11): 2891–2904. doi:10.1158/1078-0432.Ccr-16-1025.
[112] Zhou G, Zhang F, Guo Y, Huang J, Xie Y, Yue S, et al. miR-200c enhances sensitivity of drug-resistant non-small cell lung cancer to gefitinib by suppression of PI3K/Akt signaling pathway and inhibites cell migration via targeting ZEB1. Biomed Pharmacother 2017;85:113–119. doi:10.1016/j.biopha.2016.11.100.

[113] Jin S, He J, Li J, Guo R, Shu Y, Liu P. MiR-873 inhibition enhances gefitinib resistance in non-small cell lung cancer cells by targeting glioma-associated oncogene homolog 1. Thorac Cancer 2018;9(10):1262–1270. doi:10.1111/1759-7714.12830.

[114] Tang X, Liang J, Zhu J, He N, Tan J. HOXA4-regulated miR-138 suppresses proliferation and gefitinib resistance in non-small cell lung cancer. Mol Genet Genomics 2019;294(1):85–93. doi:10.1007/s00438-018-1489-3.

[115] Xie WB, Liang LH, Wu KG, Wang LX, He X, Song C, et al. MiR-140 Expression Regulates Cell Proliferation and Targets PD-L1 in NSCLC. Cell Physiol Biochem 2018;46(2):654–663. doi:10.1159/000488634.

[116] Ulivi P, Petracci E, Marisi G, Baglivo S, Chiari R, Billi M, et al. Prognostic Role of Circulating miRNAs in Early-Stage Non-Small Cell Lung Cancer. J Clin Med 2019;8(2):131. doi:10.3390/jcm8020131.

[117] Gao X, Zhao H, Diao C, Wang X, Xie Y, Liu Y, et al. miR-455-3p serves as prognostic factor and regulates the proliferation and migration of non-small cell lung cancer through targeting HOXB5. Biochem Biophys Res Commun 2018;495(1):1074–1080. doi:10.1016/j.bbrc.2017.11.123.

[118] Li Y, Cui X, Li Y, Zhang T, Li S. Upregulated expression of miR-421 is associated with poor prognosis in non-small-cell lung cancer. Cancer Manag Res 2018;10:2627–2633. doi:10.2147/cmar.S167432.

[119] Zhang L, Lin J, Ye Y, Oba T, Gentile E, Lian J, et al. Serum MicroRNA-150 Predicts Prognosis for Early-Stage Non-Small Cell Lung Cancer and Promotes Tumor Cell Proliferation by Targeting Tumor Suppressor Gene SRCIN1. Clin Pharmacol Ther 2018;103(6):1061–1073. doi:10.1002/cpt.870.