Molecular Therapy
Nucleic Acids
Review

miR-206/133b Cluster: A Weapon against Lung Cancer?

Jing-Yu Pan,[1,4] Cheng-Cao Sun,[1,4] Zhuo-Yue Bi,[2,4] Zhen-Long Chen,[3,4] Shu-Jun Li,[1,3] Qing-Qun Li,[1] Yu-Xuan Wang,[1] Yong-Yi Bi,[1] and De-Jia Li[1]

[1]Department of Occupational and Environmental Health, School of Public Health, Wuhan University, Wuhan 430071 Hubei, P.R. China; [2]Hubei Provincial Key Laboratory for Applied Toxicology (Hubei Provincial Academy for Preventive Medicine), Wuhan 430079 Hubei, P.R. China; [3]Wuhan Hospital for the Prevention and Treatment of Occupational Diseases, Wuhan 430022 Hubei, P.R. China

Lung cancer is a deadly disease that ends numerous lives around the world. MicroRNAs (miRNAs) are a group of non-coding RNAs involved in a variety of biological processes, such as cell growth, organ development, and tumorigenesis. The miR-206/133b cluster is located on the human chromosome 6p12.2, which is essential for growth and rebuilding of skeletal muscle. The miR-206/133b cluster has been verified to be dysregulated and plays a crucial role in lung cancer. miR-206 and miR-133b participate in lung tumor cell apoptosis, proliferation, migration, invasion, angiogenesis, drug resistance, and cancer treatment. The mechanisms are sophisticated, involving various target genes and molecular pathways, such as MET, EGFR, and the STAT3/HIF-1α/VEGF signal pathway. Hence, in this review, we summarize the role and potential mechanisms of the miR-206/133b cluster in lung cancer.

Lung cancer is a severe disease with a poor prognosis, giving rise to a growing body of patient deaths. In China, many people lose their life as a result of cancers, and lung cancer is the primary cause of them. About 610,000 individuals were estimated to die of lung cancer in 2015, contributing to a grave disease burden.[1] Lung cancer can be divided into four leading types according to histologic pathology: large cell carcinoma, small cell carcinoma, squamous cell carcinoma, and adenocarcinoma.[2] Nonetheless, lung cancer is also historically classified into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) in terms of the diverse clinical presentation, metastasis, and sensitivity to therapy.[2–4] Approximately 80% patients with lung cancer could be diagnosed as having NSCLC, and only 10%–15% of patients can survive for 5 years or longer.[5] Nowadays, patients with lung cancer are predominantly given chemotherapy to relieve or control their conditions. The effect is unsatisfactory; hence, it is imperative to investigate novel and helpful approaches against lung cancer.

MicroRNAs (miRNAs) 20–25 nucleotides in length belong to small non-coding RNAs and make sense in regulation for the targeted gene by targeting a specific 3′ UTR of mRNAs.[6–8] Accumulating evidence indicates that miRNAs participate in diverse cancers, including lung cancer. miR-187-3p functioned as a tumor suppressor in lung cancer, where it can repress proliferation, migration, and invasion, as well as enhance cell apoptosis by targeting oncogene BCL6.[9] miR-326 and miR-329 are both downregulated in patients' tissue and cell lines and act in an anticancer role in NSCLC.[10,11] However, some cancer-associated miRNAs might act as cancer promoters, and miR-17-92 cluster is an example. miR-17-92 regulated lung tumorigenesis by directly targeting hypoxia-inducible factor 1α (HIF-1α), and upregulation of c-*myc* resulted in induction of miR-17-92 and downregulation of HIF-1α.[12,13] Furthermore, miR-346 has been revealed as a tumor enhancer by modulating the XPC/ERK/Snail/E-cadherin pathway in NSCLC, as well as being associated with poor prognosis.[14] Therefore, various miRNAs may have different functions in human cancer for reasons that remain unknown.

The miR-206/133b cluster is located on the human chromosome 6p12.2, which is essential for growth and rebuilding of skeletal muscle; it is not expressed in the heart.[15] This miRNA cluster includes not only so-called the myoRNAs miR-206 and miR-133b but also the long non-coding RNA linc-MD1, which plays a pivotal part in muscle differentiation.[16] Nonetheless, linc-MD1 has not been deeply investigated, and there is no evidence showing that this long non-coding RNA participates in human diseases, including human cancer. Accordingly, the miR-206/133b cluster specifically refers to miR-206 and miR-133b in this paper. It has been reported that miR-206/133b can be discovered in slow myofibers in adult muscle, and its expression is regulated by a network of myogenic genes, such as MyoD, a kind of muscle regulatory factor (MRF).[17,18] Moreover, it was disclosed as being involved in immune response and may be a biomarker for a Th17-type immune reaction in T cells.[19] In addition, these miRNAs appeared to dysregulate a multitude of human cancers, including breast cancer,[20] cervical carcinoma,[21] colon cancer,[22] and lung cancer.[19] Both miR-206 and miR-133b are significantly downregulated in lung cancer (Table 1), suggesting they may play parts in lung tumorigenesis.

http://dx.doi.org/10.1016/j.omtn.2017.06.002.

[4]These authors contributed equally to this work.

Correspondence: De-Jia Li, No. 115 Donghu Road, Wuchang District, Wuhan, 430071 Hubei, P.R. China.
E-mail: lodjlwhu@sina.com
Correspondence: Cheng-Cao Sun, No. 115 Donghu Road, Wuchang District, Wuhan, 430071 Hubei, P.R. China.
E-mail: chengcaosun@whu.edu.cn

Table 1. Dysregulation of the miR-206/133b Cluster in Lung Cancer

Lung Cancer Type	miRNA	Expression	Target Genes	Tissue/Cells	Reference
LAC	miR-206	down	Smad3	cells	37
NSCLC	miR-206	down	14-3-3z	cells	46
Lung cancer[a]	miR-206	down	CCL2, VEGFA	cells	48
NSCLC	miR-206	down	MET	both	31,57,68
NSCLC	miR-206	down	c-Met	both	47
NSCLC	miR-206	down	c-Met, Bcl2	both	34
NSCLC	miR-206	down	SOX9	both	58
LSCC	miR-206	down	MET, EGFR	cells	30
LAC	miR-206	down	G6PD, PGD, TKT, GPD2	cells	39
NSCLC	miR-206	down	–	both	56,78
LAC	miR-206	down	–	cells	77
NSCLC	miR-133b	down	FSCN1	cells	60
NSCLC	miR-133b	down	PKM2	cells	72
NSCLC	miR-133b	down	EGFR	both	32
LAC	miR-133b	down	MCL-1, BCL2L2	both	33
Lung cancer[a]	both[b]	down	–	–	80
LAC	miR-133b	down	–	both	40
NSCLC	miR-133b	down	–	tissue	61
Lung cancer[a]	miR-133b	down	–	tissue	81

LAC, lung adenocarcinoma; LSCC, lung squamous cell carcinoma; PKM2, pyruvate kinase isoform M2.
[a]Lung cancer types were not mentioned.
[b]Including miR-206 and miR-133b.

In the present review, we highlighted the function, target genes, and mechanisms of the miR-206/133b cluster in lung cancer cell apoptosis, proliferation, migration, invasion, angiogenesis, and cancer treatment to provide evidence for further investigations and the clinic in the future.

Promotion of Cell Apoptosis

Tumor cell apoptosis is regulated by a network of factors, and dysregulation of cell apoptosis is linked to a body of diseases, referring to numerous molecular pathways and proteins. Eukaryotic cells motivate caspase-7 and caspase-3 to promote apoptosis via death receptor- and mitochondria-induced signal pathways.[23–25] The B cell lymphoma (Bcl) 2 family includes three subsets: anti-apoptosis proteins such as Bcl-xL and Bcl-2, pro-apoptosis proteins such as Bak and Bax, and BH3-only proteins, which play a vital role in cell apoptosis.[26,27]

MET is the tyrosine kinase receptor of the hepatocyte growth factor (HGF) and greatly relates to tumorigenesis. Evidence shows that the MET plays a key role in p53-mediated regulation of migration and invasion through the signal pathway of phosphatidylinositol 3-kinase (PI3K)-AKT and mTOR.[28] Epidermal growth factor receptor (EGFR) tightly associates with NSCLC and plays a critical part in terms of patients' chemotherapy.[29] In lung squamous cell carcinoma, miR-206 was identified to be decreased and upregulation of it markedly boosted cell apoptosis and gave rise to cell-cycle arrest.[30] Further investigations confirmed that MET and EGFR were the direct targets of miR-206, and the signal pathway was inhibition of their downstream phosphorylation of ERK1/2 and AKT.[30] In addition, Chen et al.[31] discovered miR-206 was able to significantly reduce expression of MET, and it was demonstrated as a direct target of miR-206 in lung adenocarcinoma (LAC) cell. However, flow cytometry assay suggested miR-206 slightly led to HCC827 and A549 cell death in the early stage, whereas the HCC827 cell apoptosis rate was remarkably higher after treatment of miR-206 than in the negative control group at a later time. The similar phenomenon was not observed in A549 cells in the late stage.[31] miR-133b was also disclosed to correlate with tumor stages, visceral pleura, migration, and EGFR mRNA expression, as well as to contributed to lung cancer cell apoptosis in NSCLC.[32] Furthermore, EGFR was verified as a qualified target gene of miR-133b by combining bioinformatic prediction with luciferase reporter assay. The signal pathway was also repression of the EGFR downstream phosphorylation of ERK1/2 and AKT.[32] These findings suggested the miR-206/133b-EGFR pathway plays a critical role in lung cancer. Crawford et al.[33] also demonstrated the level of miR-133b was the lowest in 41 miRNAs using a high-throughput qRT-PCR assay in lung tumor tissues. Myeloid cell leukemia 1 (MCL-1) and B cell CLL/lymphoma 2 like 2 (BCL2L2), the members of the BCL-2 family, were validated as the targets of miR-133b. In addition, upregulation of miR-133b induced a small degree of LAC

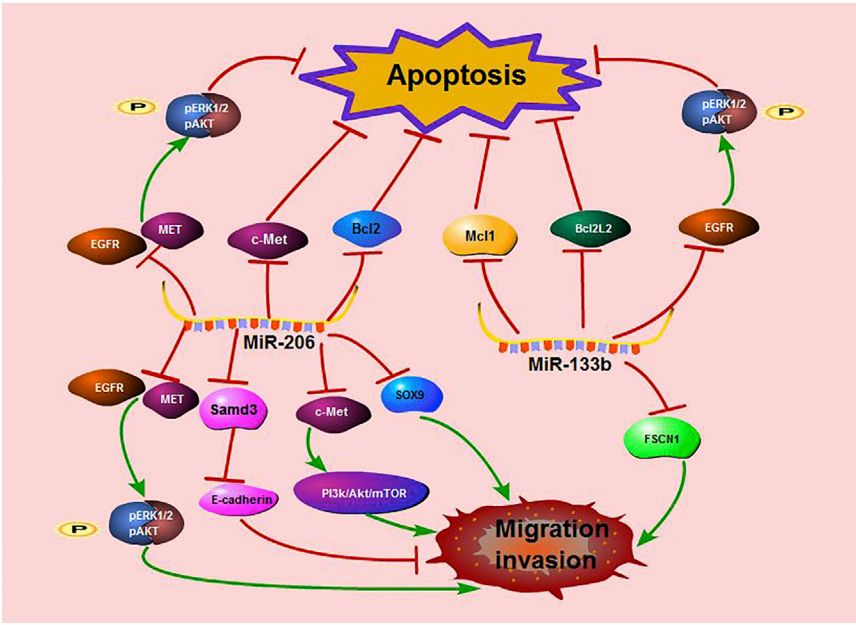

Figure 1. miR-133b/206 Associates with Various Genes Mediating NSCLC Cell Migration and Invasion
miR-206 promoted lung cancer cell apoptosis by targeting c-Met and Bcl2, as well as governed EGFR, MET, and its downstream phosphorylation of ERK1/2 and AKT. Likewise, miR-133b boosted lung cancer cell apoptosis by suppressing expression of MCL1, BCL2L2, and attenuated EGFR and its downstream phosphorylation of ERK1/2 and AKT. Furthermore, miR-206 inhibited lung cancer cell migration and invasion by repressing SOX9 and Smad3 and upregulating E-cadherin, meanwhile blocked EGFR, MET, and its downstream phosphorylation of ERK1/2 and AKT, as well as antagonized c-Met and the PI3K/Akt/mTOR pathway. miR-133b repressed FSCN1, contributing to the blockage of lung cancer cell migration and invasion.

cell apoptosis and diminished expression of MCL-1 and BCL2L2.[33] In another investigation, c-Met, Bcl2, and cyclin D1 were overexpressed in lung cancer tissues, and downregulation of them enhanced NSCLC cell (SK-MES-1 cell and A549 cell) apoptosis.[34] Further assays verified that both Bcl-2 and c-Met were the appropriate targets of miR-206, and miR-206 prominently reduced their levels in NSCLC.[34]

Taking all these findings into consideration, we suppose the miR-206/133b cluster might be a promoter in lung cancer cell apoptosis. The relationship between these lung cancer-related miRNAs and corresponding targets or signaling pathway are briefly summarized in Figure 1.

Inhibition of Cell Proliferation

It is generally known that cell proliferation plays a critical role in tumorigenesis and tumor progression. Cells lack some factors of control and regulation, giving rise to the development of neoplasms. There is a growing body of evidence showing that the miR-206/133b cluster participates in a great deal of tumor cell proliferation. Ren et al.[35] revealed that miR-206 could suppress colorectal cancer cell proliferation by targeting formin-like 2 (FMNL2), which was validated as an emerging member of diaphanous-related formins (DRFs). miR-133b was found to be decreased in renal cell carcinoma cells, and restoration of its expression significantly repressed cell proliferation by regulating matrix metallopeptidase 9 (MMP-9).[36]

Smad3, a transcription factor, is characterized as a key regulator in the TGF-β1 (transforming growth factor β1)/Smad signal pathway, which involves in tumorigenesis.[37,38] Zhang et al.[37] reported that the TGF-β1 could lessen the expression of miR-140 and miR-206, and further study demonstrated these miRNAs acted as tumor inhibitors in the LAC cell by targeting Smad3 and affecting the TGF-β1-related pathway, contributing to repression of cell proliferation. They also revealed that these miRNAs associated with tribbles homolog 2 (TRIB2) in inhibition of cell proliferation in vivo, but no further investigations were performed to confirm whether the TRIB2 was a target of miR-206.[37] In addition, miR-206 tightly correlated with NRF2 (nuclear factor erythroid-2-related factor 2) and the pentose phosphate pathway, and all of them (NRF2 and pentose phosphate pathway) were dramatically dysregulated in lung tumor.[39] NRF2 was able to downregulate the expression of miR-206 and modulate the metabolic flux of lung cancer cells by affecting fatty acid synthesis, the tricarboxylic acid cycle, and the pentose phosphate pathway.[39] miR-206 was uncovered to target the pentose phosphate pathway genes (G6PD, PGD, TKT, and GPD2), reducing pentose phosphate pathway-related NADPH production and ribose synthesis and suppression of the growth of the H1437 cell and A549 cell. The analogous role of miR-206 was observed in vivo.[39] Our research group disclosed that restoration of miR-206 does not merely boost lung cancer cell apoptosis but also represses proliferation by binding to Bcl-2 and c-Met mRNA.[34] In LAC, Zhang et al.[40] discovered four miRNAs were dramatically dysregulated via miRNA microarray and qRT-PCR assays, including miR-133b. Upregulation of miR-133b significantly suppressed SPC-A1 cell and A549 cell proliferation, whereas there was no function to migration and invasion of these cancer cells.[40]

In this section, evidence shows that the miR-206/133b cluster acts as a suppressor in lung cancer cell proliferation. The link between these lung cancer-related miRNAs and corresponding targets or signaling pathway was briefly generalized in Figure 2.

Blocking Tumor Angiogenesis

Angiogenesis is a crucial process in tumorigenesis and tumor development. If there are effective and credible approaches to treatment that blocks angiogenesis, a great deal of patients will live longer.[41] The mechanisms of angiogenesis are sophisticated and complicated, involving anti-angiogenic factors such as Notch molecular pathway,

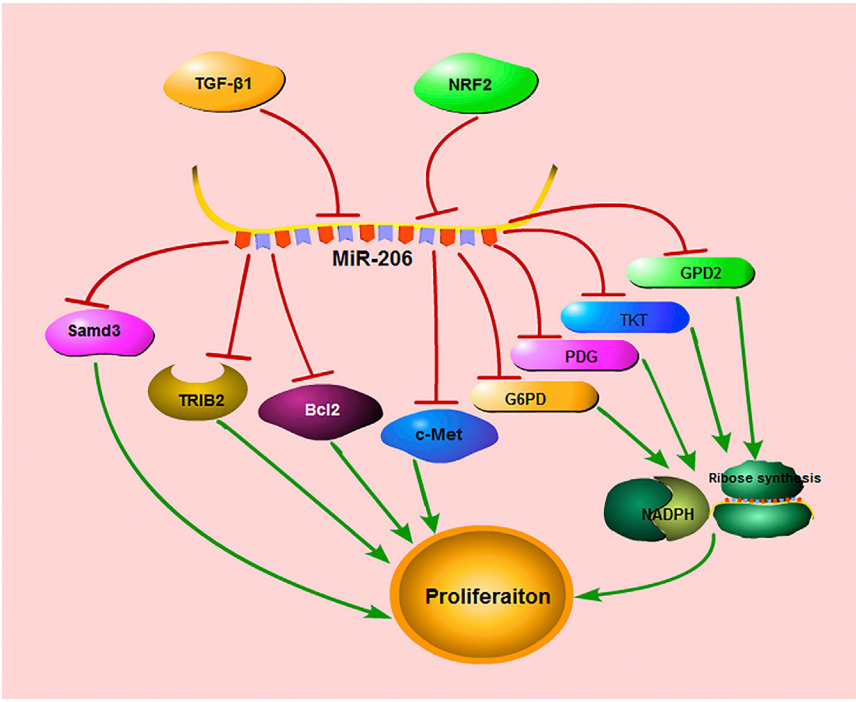

Figure 2. miR-206 Associates with Various Genes Mediating NSCLC Cell Proliferation

NRF2 could decrease miR-206 expression, while miR-206 was able to repress the pentose phosphate pathway genes (G6PD, PGD, TKT, and GPD2), reducing pentose phosphate pathway-related NADPH production and ribose synthesis and then giving rise to blockage of lung cancer cell proliferation. In addition, TGF-β1 enabled miR-206 to decline, whereas restoration of miR-206 significantly suppressed the level of Samd3 and TRIB2, leading to inhibit proliferation. However, miR-206 also directly repressed Bcl2 and c-Met expression, contributing to inhibition of cell proliferation in lung cancer.

matrix metalloproteinases, and pro-angiogenic factors such as FGF (fibroblast growth factor) and VEGF (vascular endothelial growth factor).[42,43] Increasingly, investigations have shown that miRNAs associate with tumor angiogenesis. For instance, Tu et al.[44] uncovered that upregulation of miR-497 markedly repressed tumor angiogenesis by targeting VEGFR2, a key receptor of VEGF.

Furthermore, miR-206 was disclosed to tightly correlate with angiogenesis in lung cancer. Previous findings suggested that the 14-3-3 family dysregulated and played a critical role in NSCLC.[45] Xue et al.[46] found the expression of 14-3-3z was increased in lung cancer cell lines, which could induce tumor angiogenesis in vivo and in vitro. Nevertheless, miR-206 was discovered to play an inverse role, suppressing lung tumor angiogenesis.[46] The underlying mechanism of miR-206-regulated angiogenesis was suppression of the 14-3-3z/STAT3/HIF-1α/VEGF signaling pathway.[46] Similarly, the relationship among miR-206 and HGF-induced angiogenesis was investigated.[47] HGF was able to induce tubules formation and metastasis of human umbilical vein endothelial cells (HUVECs), whereas miR-206 dramatically repressed it and the mechanism correlated with blocking PI3k/Akt/mTOR molecular pathways.[47] In addition, Shen et al.[48] investigated the underlying mechanism by which normal fibroblasts (NFs) transform into cancer-associated fibroblasts (CAFs) in lung cancer. They found CAFs promoted tumor growth and angiogenesis, and miR-206 inhibited the conversion of NFs to CAFs by targeting VEGFA/CCL2.[48]

It has been reported that HUVECs qualified as a model of angiogenesis in in vitro study. In addition, miR-133 could enhance HUVEC apoptosis and inhibit proliferation and migration by modulating FGF receptor 1.[41] Nevertheless, up to now, miR-133b has not been reported to participate in lung cancer angiogenesis. Whether miR-133b plays an analogous role to miR-206 in lung tumor angiogenesis needs to be determined in the future.

Repression of Migration and Invasion

Tumor cell migration and invasion are critical processes in cancer metastasis and are controlled by complicated factors. The epithelial-to-mesenchymal transition (EMT) is a well-established element in the transformation of early-stage tumors into advanced cancer. Decreased expression of E-cadherin, a calcium-dependent transmembrane glycoprotein, is a key hallmark in EMT.[49] E-selectin targeting PEGylated-thioaptamer is able to block breast cancer metastasis.[50] Accumulating evidence suggests that dysregulation of E-cadherin results in tumor metastasis and an unsatisfactory prognosis in a variety of human tumors.[51–53] In addition, it has been reported that miRNAs tightly correlate with EMT in cancer metastasis.[54,55]

HGF was able to induce EMT and contribute to migration and invasion of lung cancer A549 and 95D cells, while miR-206 markedly blocked HGF-induced EMT, as well as attenuating lung cancer cell migration and invasion by modulating c-Met and its downstream PI3k/Akt/mTOR molecular pathway.[47] Wang et al.[56] also discovered miR-206 was downregulated and that overexpression of it could diminish the metastasis of the 95D cell. However, the potential targets and mechanisms of it were not further investigated. miR-206 and miR-140 have been previously described to suppress lung cancer cell proliferation. They also have been confirmed to inhibit LAC cell metastasis, which could upregulate the level of E-cadherin by targeting Smad-3 and triggering TRIB2-related activity.[37] Furthermore, miR-206 was found to inhibit lung cancer cell migration and invasion by regulating MET.[31,34,57] Mataki et al.[30] pointed out miR-206 attenuated metastasis of lung squamous cell carcinoma EBC-1 cells via wound healing and Matrigel invasion assays through regulation of MET and the EGFR downstream signaling pathway. These findings indicates that miRNA-mediated MET plays a critical role in lung

cancer cell migration and invasion. In addition, miR-206-related SOX9 (sex-determining region Y [SRY] box 9) activity participated in lung cancer cell migration and invasion.[58]

Fascin1 (FSCN1), a member of FSCN family, has been validated to enhance NSCLC cell migration and invasion and have no effect on tumor cell proliferation.[59] Yang et al.[60] uncovered that FSCN1 was a direct target of miR-133b and increased in NSCLC cells. As in previous investigations, FSCN1 significantly promoted NSCLC cell migration and invasion, whereas miR-133b played an inverse role when compared with the FSCN1.[60] In addition, low expression of miR-133b dramatically associated with lymph nodes metastasis and an advanced stage in NSCLC.[61] However, the mechanisms and other functions of miR-133b were not further investigated. The relationship between these lung cancer-related miRNAs and corresponding targets or signaling pathway were briefly summarized in Figure 1.

Treatment and Prognosis

It is widely acknowledged that chemotherapy is a pivotal approach to antagonizing a tumor; however, it seems to generate drug resistance and has undesirable prognosis and complications. With the relationship between miRNAs and human cancer gradually uncovered, miRNA-based therapy may be an underlying approach in the future. For instance, miR-34 has been the first miRNA mimic for cancer treatment in a phase I clinical,[62] which was also considered a cancer repressor by regulating multitudes of genes and molecular pathways, such as the Notch molecular pathway, c-MYC, and CDK6.[63] Sorafenib, a well-recognized medicine for patients with advanced hepatocarcinoma, has been verified to give rise to elevate the expression of miR-423-5p in hepatocarcinoma patients' serum, and miR-423-5p was detected that promoted hepatocarcinoma cell autophagy.[64] It has been reported that the microtubule-associated protein (MAP) kinase and interacting kinase aptamers inhibit tumor cell growth, colony formation, and migration in breast cancer.[65] The miR-29b-p53-mediated pathway is regard as one of the most critical modulated pathways in carcinomas therapeutics. LK-L1C/K6W/L8C, a novel synthesized amphiphilic peptide, has been demonstrated as being able to induce cancer cell apoptosis by the miR-29b-p53-mediated pathway.[66]

Cisplatin, a well-established chemotherapeutic drug, is commonly applied for lung cancer treatment. Nonetheless, it has been reported that lung cancer patients always trigger cisplatin resistance in clinical application.[67] Cisplatin-resistant H1299/DDP and A549/DDP cells were inclined to appear EMT, invasion, and migration.[68] Low expression of miR-206 was observed in cisplatin-resistant LAC cells, whereas re-expressed miR-206 facilitated the cells to be sensitive to cisplatin treatment and antagonized EMT, invasion, and migration.[68] Further assays revealed miR-206 blocked EMT, cell metastasis, and cisplatin resistance by targeting MET and repressing its downstream PI3k/Akt/mTOR molecular pathway.[68] PF-04691502, a dual PI3K/mTOR suppressor, in combination with VEGF small interfering RNA (siRNA), blocked NSCLC, which may be useful for lung cancer patient therapy.[69] Moreover, PCTAIRE1 siRNA-lipid nanoparticles reduced tumor growth significantly compared with the scramble control group.[70] In addition, Liu et al.[32] found miR-133b was able to promote sensitivity of NSCLC cells toward gefitinib chemotherapy, of which mechanisms may include the EGFR-related pathway. Gemcitabine, another chemotherapeutic agent, combined with platinum treatment, has been widely applied in advanced NSCLC.[71] Evidence suggested gemcitabine combined with miR-133b mimic exhibited a remarkable effect in terms of lung cancer cell chemotherapy.[33] miR-133b was also verified to correlate with radiation therapy in lung cancer cells, and it was low expressed in radioresistant lung cancer cells.[72] Elevating expression of miR-133b contributed to radioresistant lung cancer cells being resensitive, and the relevant pathway was involved in pyruvate kinase isoform M2-mediated glycolysis.[72] In addition, Wu et al.[73] demonstrated that cationic lipids combined with pre-miR-133b significantly elevated the level of mature miR-133b in the lung cancer A549 cell and in the mouse model. This study may greatly contribute to how miRNA-based treatment can be more efficient in the future.

Furthermore, the miR-206/133b cluster correlates with lung cancer patients' prognosis and survival. Zhang et al.[37] discovered TRIB2 was higher in lung cancer samples and linked to a poorer prognosis, whereas miR-206 could inhibited TRIB2-related activity in lung cancer cells. This investigation implied miR-206 may be beneficial for lung cancer patients' survival. Xue et al.[46] investigated a cohort of 116 NSCLC patients, studying the relationship between expression of miR-206/14-3-3z and prognosis. They disclosed that the miR-206 high/14-3-3z low group had the longest survival compared with the miR-206 low/14-3-3z high group through Kaplan-Meier survival analysis.[46] In addition, LAC patients were divided into solid subtype positive and negative groups, and the solid subtype positive group had poorer prognosis than the negative one, while miR-133b was dramatically decreased in the solid subtype positive group.[40] However, miR-133b was also found to positively associate with lung cancer patients' overall survival.[61] These findings suggested miR-133b may be beneficial for lung cancer patients' prognosis.

This section mainly generalizes the role of the miR-206/133b cluster in lung cancer treatment and prognosis. We assume that these miRNAs may facilitate drug-resistant lung cancer cells in becoming resensitive, as well as contribute to better prognosis and survival in lung cancer.

Others

Long non-coding RNAs (lncRNAs) have been reported to play pivotal roles in lung cancer progression.[74,75] Furthermore, lncRNAs are able to function as competing endogenous RNAs. For instance, the long non-coding RNA NEAT1 promoted lung cancer development by blocking miR-377-3p, resulting in the de-repression of its endogenous target E2F3.[76] RMRP, a member of the lncRNAs, was found to inhibit expression of miR-206 and elevate the level of SOX9, FMNL2, and Kirsten rat sarcoma viral oncogene (KRAS) in lung cancer.[77] Further experiments confirmed this lncRNA played an oncogenic function by targeting miR-206 and promoting expression of

SOX9, FMNL2, and KRAS.[77] The crosstalk between lncRNAs and miRNAs may be further explored and contribute to uncover the unrecognized fields of cancer.

Cui et al.[78] discovered eight so-called hub genes (HSPD1, POLA1, SMARCA4, ENO1, HSPA5, CDC42, CTSD, and CALR) were underlying functional targets of miR-206 in the A549 cell line via quantitative proteomics and protein network analysis. Nevertheless, the definite function and link between these genes and miR-206 has not been investigated in lung cancer. Until now, it has not been reported that the miR-206/133b cluster plays a part in circulating miRNAs in lung cancer patients. 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), a critical component of tobacco, could be a high risk for lung carcinogenesis.[79] In NNK-induced rat lung tumor experiments, both miR-206 and miR-133b were found to be upregulated in the rats' serum in the early phase of NNK-induced lung tumorigenesis.[80] However, serum miR-206 and miR-133b were remarkably decreased in a late-stage study, which corresponded with the result in NNK-induced rat lung tumor tissues.[80] If these findings are convincing and scientific, we hypothesize that rats antagonize NNK-induced microenvironmental alteration and strike a balance, giving rise to lung cancer suppressor-associated miRNAs that elevated early. Nonetheless, after tumor formulation, some mechanisms and factors have been repressed or impaired, and then these miRNAs appear to be downregulated. Further investigations are required to determine whether miR-133b and miR-206 are diagnosed biomarkers in lung cancer patients.

Conclusions

In this review, we summarized the roles and mechanisms of the miR-206/133b cluster in lung cancer. We discovered miR-206 and miR-133b could promote cell apoptosis, repress cell proliferation, block tumor angiogenesis, and inhibit cell migration and invasion in lung cancer. Moreover, we uncovered that these miRNAs boosted drug-resistant and radioresistant lung cancer cells to be resensitive, and upregulation of these miRNAs might be beneficial for lung cancer patients' prognosis and survival. The mechanisms were sophisticated, including MET, Smad3, EGFR, and 14-3-3z-associated signaling pathways. Altogether, these findings indicated the miR-206/133b cluster acted as a suppressor in lung cancer by targeting diverse genes and related molecular pathways, which might provide evidence for clinical applications and further study.

AUTHOR CONTRIBUTIONS

J.-Y.P. was responsible for conceiving, designing, and writing part of the project, while C.-C.S., Z.-Y.B., and Z.-L.C. conceived, designed, and wrote the remainder of the project, in addition to checking and modifying the manuscript. S.-J.L., Q.-Q.L., Y.-X.W., and Y.-Y.B. proposed some independent ideas to improve the manuscript. D.-J.L. and C.-C.S. are the principals of our research group and the corresponding authors.

CONFLICTS OF INTEREST

The authors disclose no potential conflicts of interest.

ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (No. 81271943 to D.-J.L.), the Plan for the Scientific and Technological Innovation Team of the High-Tech Industries of Wuhan Municipal Science and Technology Bureau (No. 2015070504020219 to D.-J.L.), the Fundamental Research Funds for the Central Universities (No. 2015305020202 to C.-C.S.), and the China Postdoctoral Science Foundation (No. BX201700178 to C.-C.S.). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

REFERENCES

1. Chen, W., Zheng, R., Baade, P.D., Zhang, S., Zeng, H., Bray, F., Jemal, A., Yu, X.Q., and He, J. (2016). Cancer statistics in China, 2015. CA Cancer J. Clin. *66*, 115–132.
2. Travis, W.D. (2004). Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart (IARC Press).
3. Travis, W.D. (2011). Pathology of lung cancer. Clin. Chest Med. *32*, 669–692.
4. Rossi, G., Mengoli, M.C., Cavazza, A., Nicoli, D., Barbareschi, M., Cantaloni, C., Papotti, M., Tironi, A., Graziano, P., Paci, M., et al. (2014). Large cell carcinoma of the lung: clinically oriented classification integrating immunohistochemistry and molecular biology. Virchows Arch. *464*, 61–68.
5. Beadsmoore, C.J., and Screaton, N.J. (2003). Classification, staging and prognosis of lung cancer. Eur. J. Radiol. *45*, 8–17.
6. Fabian, M.R., Sonenberg, N., and Filipowicz, W. (2010). Regulation of mRNA translation and stability by microRNAs. Annu. Rev. Biochem. *79*, 351–379.
7. Grosswendt, S., Filipchyk, A., Manzano, M., Klironomos, F., Schilling, M., Herzog, M., Gottwein, E., and Rajewsky, N. (2014). Unambiguous identification of miRNA:target site interactions by different types of ligation reactions. Mol. Cell *54*, 1042–1054.
8. Liu, X., Zheng, Q., Vrettos, N., Maragkakis, M., Alexiou, P., Gregory, B.D., and Mourelatos, Z. (2014). A microRNA precursor surveillance system in quality control of microRNA synthesis. Mol. Cell *55*, 868–879.
9. Sun, C., Li, S., Yang, C., Xi, Y., Wang, L., Zhang, F., and Li, D. (2016). MicroRNA-187-3p mitigates non-small cell lung cancer (NSCLC) development through down-regulation of BCL6. Biochem. Biophys. Res. Commun. *471*, 82–88.
10. Sun, C., Huang, C., Li, S., Yang, C., Xi, Y., Wang, L., Zhang, F., Fu, Y., and Li, D. (2016). Hsa-miR-326 targets CCND1 and inhibits non-small cell lung cancer development. Oncotarget *7*, 8341–8359.
11. Sun, C.C., Li, S.J., Zhang, F., Pan, J.Y., Wang, L., Yang, C.L., Xi, Y.Y., and Li, J. (2016). Hsa-miR-329 exerts tumor suppressor function through down-regulation of MET in non-small cell lung cancer. Oncotarget *7*, 21510–21526.
12. Joshi, P., Middleton, J., Jeon, Y.J., and Garofalo, M. (2014). MicroRNAs in lung cancer. World J. Methodol. *4*, 59–72.
13. Taguchi, A., Yanagisawa, K., Tanaka, M., Cao, K., Matsuyama, Y., Goto, H., and Takahashi, T. (2008). Identification of hypoxia-inducible factor-1 alpha as a novel target for miR-17-92 microRNA cluster. Cancer Res. *68*, 5540–5545.
14. Sun, C.C., Li, S.J., Yuan, Z.P., and Li, D.J. (2016). MicroRNA-346 facilitates cell growth and metastasis, and suppresses cell apoptosis in human non-small cell lung cancer by regulation of XPC/ERK/Snail/E-cadherin pathway. Aging (Albany NY) *8*, 2509–2524.
15. Boettger, T., Wüst, S., Nolte, H., and Braun, T. (2014). The miR-206/133b cluster is dispensable for development, survival and regeneration of skeletal muscle. Skelet. Muscle *4*, 23.
16. Cesana, M., Cacchiarelli, D., Legnini, I., Santini, T., Sthandier, O., Chinappi, M., Tramontano, A., and Bozzoni, I. (2011). A long noncoding RNA controls muscle differentiation by functioning as a competing endogenous RNA. Cell *147*, 358–369.
17. Rao, P.K., Kumar, R.M., Farkhondeh, M., Baskerville, S., and Lodish, H.F. (2006). Myogenic factors that regulate expression of muscle-specific microRNAs. Proc. Natl. Acad. Sci. USA *103*, 8721–8726.

18. Sweetman, D., Goljanek, K., Rathjen, T., Oustanina, S., Braun, T., Dalmay, T., and Münsterberg, A. (2008). Specific requirements of MRFs for the expression of muscle specific microRNAs, miR-1, miR-206 and miR-133. Dev. Biol. *321*, 491–499.

19. Mitchelson, K.R., and Qin, W.Y. (2015). Roles of the canonical myomiRs miR-1, -133 and -206 in cell development and disease. World J. Biol. Chem. *6*, 162–208.

20. Min, W., Wang, B., Li, J., Han, J., Zhao, Y., Su, W., Dai, Z., Wang, X., and Ma, Q. (2014). The expression and significance of five types of miRNAs in breast cancer. Med. Sci. Monit. Basic Res. *20*, 97–104.

21. Qin, W., Dong, P., Ma, C., Mitchelson, K., Deng, T., Zhang, L., Sun, Y., Feng, X., Ding, Y., Lu, X., et al. (2012). MicroRNA-133b is a key promoter of cervical carcinoma development through the activation of the ERK and AKT1 pathways. Oncogene *31*, 4067–4075.

22. Parasramka, M.A., Dashwood, W.M., Wang, R., Saeed, H.H., Williams, D.E., Ho, E., and Dashwood, R.H. (2012). A role for low-abundance miRNAs in colon cancer: the miR-206/Krüppel-like factor 4 (KLF4) axis. Clin. Epigenetics *4*, 16.

23. Hirata, H., Takahashi, A., Kobayashi, S., Yonehara, S., Sawai, H., Okazaki, T., Yamamoto, K., and Sasada, M. (1998). Caspases are activated in a branched protease cascade and control distinct downstream processes in Fas-induced apoptosis. J. Exp. Med. *187*, 587–600.

24. Villa, P., Kaufmann, S.H., and Earnshaw, W.C. (1997). Caspases and caspase inhibitors. Trends Biochem. Sci. *22*, 388–393.

25. Slee, E.A., Harte, M.T., Kluck, R.M., Wolf, B.B., Casiano, C.A., Newmeyer, D.D., Wang, H.G., Reed, J.C., Nicholson, D.W., Alnemri, E.S., et al. (1999). Ordering the cytochrome c-initiated caspase cascade: hierarchical activation of caspases-2, -3, -6, -7, -8, and -10 in a caspase-9-dependent manner. J. Cell Biol. *144*, 281–292.

26. Llambi, F., Moldoveanu, T., Tait, S.W., Bouchier-Hayes, L., Temirov, J., McCormick, L.L., Dillon, C.P., and Green, D.R. (2011). A unified model of mammalian BCL-2 protein family interactions at the mitochondria. Mol. Cell *44*, 517–531.

27. García-Sáez, A.J. (2012). The secrets of the Bcl-2 family. Cell Death Differ. *19*, 1733–1740.

28. Moumen, A., Patané, S., Porras, A., Dono, R., and Maina, F. (2007). Met acts on Mdm2 via mTOR to signal cell survival during development. Development *134*, 1443–1451.

29. Hirsch, F.R., Varella-Garcia, M., Cappuzzo, F., McCoy, J., Bemis, L., Xavier, A.C., Dziadziuszko, R., Gumerlock, P., Chansky, K., West, H., et al. (2007). Combination of EGFR gene copy number and protein expression predicts outcome for advanced non-small-cell lung cancer patients treated with gefitinib. Ann. Oncol. *18*, 752–760.

30. Mataki, H., Seki, N., Chiyomaru, T., Enokida, H., Goto, Y., Kumamoto, T., Machida, K., Mizuno, K., Nakagawa, M., and Inoue, H. (2015). Tumor-suppressive microRNA-206 as a dual inhibitor of MET and EGFR oncogenic signaling in lung squamous cell carcinoma. Int. J. Oncol. *46*, 1039–1050.

31. Chen, X., Tong, Z.K., Zhou, J.Y., Yao, Y.K., Zhang, S.M., and Zhou, J.Y. (2016). MicroRNA-206 inhibits the viability and migration of human lung adenocarcinoma cells partly by targeting MET. Oncol. Lett. *12*, 1171–1177.

32. Liu, L., Shao, X., Gao, W., Zhang, Z., Liu, P., Wang, R., Huang, P., Yin, Y., and Shu, Y. (2012). MicroRNA-133b inhibits the growth of non-small-cell lung cancer by targeting the epidermal growth factor receptor. FEBS J. *279*, 3800–3812.

33. Crawford, M., Batte, K., Yu, L., Wu, X., Nuovo, G.J., Marsh, C.B., Otterson, G.A., and Nana-Sinkam, S.P. (2009). MicroRNA 133B targets pro-survival molecules MCL-1 and BCL2L2 in lung cancer. Biochem. Biophys. Res. Commun. *388*, 483–489.

34. Sun, C., Liu, Z., Li, S., Yang, C., Xue, R., Xi, Y., Wang, L., Wang, S., He, Q., Huang, J., et al. (2015). Down-regulation of c-Met and Bcl2 by microRNA-206, activates apoptosis, and inhibits tumor cell proliferation, migration and colony formation. Oncotarget *6*, 25533–25574.

35. Ren, X.L., He, G.Y., Li, X.M., Men, H., Yi, L.Z., Lu, G.F., Xin, S.N., Wu, P.X., Li, Y.L., Liao, W.T., et al. (2016). MicroRNA-206 functions as a tumor suppressor in colorectal cancer by targeting FMNL2. J. Cancer Res. Clin. Oncol. *142*, 581–592.

36. Wu, D., Pan, H., Zhou, Y., Zhou, J., Fan, Y., and Qu, P. (2014). MicroRNA-133b downregulation and inhibition of cell proliferation, migration and invasion by targeting matrix metallopeptidase-9 in renal cell carcinoma. Mol. Med. Rep. *9*, 2491–2498.

37. Zhang, Y.X., Yan, Y.F., Liu, Y.M., Li, Y.J., Zhang, H.H., Pang, M., Hu, J.X., Zhao, W., Xie, N., Zhou, L., et al. (2016). Smad3-related miRNAs regulated oncogenic TRIB2 promoter activity to effectively suppress lung adenocarcinoma growth. Cell Death Dis. *7*, e2528.

38. Kim, I.Y., Kim, M.M., and Kim, S.J. (2005). Transforming growth factor-beta: biology and clinical relevance. J. Biochem. Mol. Biol. *38*, 1–8.

39. Singh, A., Happel, C., Manna, S.K., Acquaah-Mensah, G., Carrerero, J., Kumar, S., Nasipuri, P., Krausz, K.W., Wakabayashi, N., Dewi, R., et al. (2013). Transcription factor NRF2 regulates miR-1 and miR-206 to drive tumorigenesis. J. Clin. Invest. *123*, 2921–2934.

40. Zhang, Y.Q., Wang, W.Y., Xue, J.X., Xu, Y., Fan, P., Caughey, B.A., Tan, W.W., Cao, G.Q., Jiang, L.L., Lu, Y., et al. (2016). MicroRNA expression profile on solid subtype of invasive lung adenocarcinoma reveals a panel of four miRNAs to be associated with poor prognosis in Chinese patients. J. Cancer *7*, 1610–1620.

41. Soufi-Zomorrod, M., Hajifathali, A., Kouhkan, F., Mehdizadeh, M., Rad, S.M., and Soleimani, M. (2016). MicroRNAs modulating angiogenesis: miR-129-1 and miR-133 act as angio-miR in HUVECs. Tumour Biol. *37*, 9527–9534.

42. Sakurai, T., and Kudo, M. (2011). Signaling pathways governing tumor angiogenesis. Oncology *81* (*Suppl 1*), 24–29.

43. Tonini, T., Rossi, F., and Claudio, P.P. (2003). Molecular basis of angiogenesis and cancer. Oncogene *22*, 6549–6556.

44. Tu, Y., Liu, L., Zhao, D., Liu, Y., Ma, X., Fan, Y., Wan, L., Huang, T., Cheng, Z., and Shen, B. (2015). Overexpression of miRNA-497 inhibits tumor angiogenesis by targeting VEGFR2. Sci. Rep. *5*, 13827.

45. Qi, W., Liu, X., Qiao, D., and Martinez, J.D. (2005). Isoform-specific expression of 14-3-3 proteins in human lung cancer tissues. Int. J. Cancer *113*, 359–363.

46. Xue, D., Yang, Y., Liu, Y., Wang, P., Dai, Y., Liu, Q., Chen, L., Shen, J., Ju, H., Li, Y., and Tan, Z. (2016). MicroRNA-206 attenuates the growth and angiogenesis in non-small cell lung cancer cells by blocking the 14-3-3ζ/STAT3/HIF-1α/VEGF signaling. Oncotarget *7*, 79805–79813.

47. Chen, Q.Y., Jiao, D.M., Wu, Y.Q., Chen, J., Wang, J., Tang, X.L., Mou, H., Hu, H.Z., Song, J., Yan, J., et al. (2016). miR-206 inhibits HGF-induced epithelial-mesenchymal transition and angiogenesis in non-small cell lung cancer via c-Met/PI3k/Akt/mTOR pathway. Oncotarget *7*, 18247–18261.

48. Shen, H., Yu, X., Yang, F., Zhang, Z., Shen, J., Sun, J., Choksi, S., Jitkaew, S., and Shu, Y. (2016). Reprogramming of normal fibroblasts into cancer-associated fibroblasts by miRNAs-mediated CCL2/VEGFA signaling. PLoS Genet. *12*, e1006244.

49. Iwatsuki, M., Mimori, K., Yokobori, T., Ishi, H., Beppu, T., Nakamori, S., Baba, H., and Mori, M. (2010). Epithelial-mesenchymal transition in cancer development and its clinical significance. Cancer Sci. *101*, 293–299.

50. Morita, Y., Kamal, M., Kang, S.A., Zhang, R., Lokesh, G.L., Thiviyanathan, V., Hasan, N., Woo, S., Zhao, D., Leslie, M., et al. (2016). E-selectin targeting PEGylated-thioaptamer prevents breast cancer metastases. Mol. Ther. Nucleic Acids *5*, e399.

51. Dorudi, S., Sheffield, J.P., Poulsom, R., Northover, J.M., and Hart, I.R. (1993). E-cadherin expression in colorectal cancer. An immunocytochemical and in situ hybridization study. Am. J. Pathol. *142*, 981–986.

52. Kowalski, P.J., Rubin, M.A., and Kleer, C.G. (2003). E-cadherin expression in primary carcinomas of the breast and its distant metastases. Breast Cancer Res. *5*, R217–R222.

53. Chan, A.O., Chu, K.M., Lam, S.K., Wong, B.C., Kwok, K.F., Law, S., Ko, S., Hui, W.M., Yueng, Y.H., and Wong, J. (2003). Soluble E-cadherin is an independent pretherapeutic factor for long-term survival in gastric cancer. J. Clin. Oncol. *21*, 2288–2293.

54. Aigner, A. (2011). MicroRNAs (miRNAs) in cancer invasion and metastasis: therapeutic approaches based on metastasis-related miRNAs. J. Mol. Med. (Berl.) *89*, 445–457.

55. Wright, J.A., Richer, J.K., and Goodall, G.J. (2010). MicroRNAs and EMT in mammary cells and breast cancer. J. Mammary Gland Biol. Neoplasia *15*, 213–223.

56. Wang, X., Ling, C., Bai, Y., and Zhao, J. (2011). MicroRNA-206 is associated with invasion and metastasis of lung cancer. Anat. Rec. (Hoboken) *294*, 88–92.

57. Chen, Q.Y., Jiao, D.M., Yan, L., Wu, Y.Q., Hu, H.Z., Song, J., Yan, J., Wu, L.J., Xu, L.Q., and Shi, J.G. (2015). Comprehensive gene and microRNA expression profiling reveals miR-206 inhibits MET in lung cancer metastasis. Mol. Biosyst. *11*, 2290–2302.

58. Zhang, Y.J., Xu, F., Zhang, Y.J., Li, H.B., Han, J.C., and Li, L. (2015). miR-206 inhibits non small cell lung cancer cell proliferation and invasion by targeting SOX9. Int. J. Clin. Exp. Med. *8*, 9107–9113.

59. Zhao, J., Zhou, Y., Zhang, Z., Tian, F., Ma, N., Liu, T., Gu, Z., and Wang, Y. (2010). Upregulated fascin1 in non-small cell lung cancer promotes the migration and invasiveness, but not proliferation. Cancer Lett. *290*, 238–247.

60. Yang, X., Lei, P., Huang, Y., Zhang, Z., and Zhang, Y. (2016). MicroRNA-133b inhibits the migration and invasion of non small cell lung cancer cells via targeting FSCN1. Oncol. Lett. *12*, 3619–3625.

61. Chen, S.W., Wang, T.B., Tian, Y.H., and Zheng, Y.G. (2015). Down-regulation of microRNA-126 and microRNA-133b acts as novel predictor biomarkers in progression and metastasis of non small cell lung cancer. Int. J. Clin. Exp. Pathol. *8*, 14983–14988.

62. Bouchie, A. (2013). First microRNA mimic enters clinic. Nat. Biotechnol. *31*, 577.

63. Misso, G., Di Martino, M.T., De Rosa, G., Farooqi, A.A., Lombardi, A., Campani, V., Zarone, M.R., Gullà, A., Tagliaferri, P., Tassone, P., and Caraglia, M. (2014). Mir-34: a new weapon against cancer? Mol. Ther. Nucleic Acids *3*, e194.

64. Stiuso, P., Potenza, N., Lombardi, A., Ferrandino, I., Monaco, A., Zappavigna, S., Vanacore, D., Mosca, N., Castiello, F., Porto, S., et al. (2015). MicroRNA-423-5p promotes autophagy in cancer cells and is increased in serum from hepatocarcinoma patients treated with sorafenib. Mol. Ther. Nucleic Acids *4*, e233.

65. García-Recio, E.M., Pinto-Díez, C., Pérez-Morgado, M.I., García-Hernández, M., Fernández, G., Martín, M.E., and González, V.M. (2016). Characterization of MNK1b DNA aptamers that inhibit proliferation in MDA-MB231 breast cancer cells. Mol. Ther. Nucleic Acids *5*, e275.

66. Kim, S., Lee, J.H., Kang, I., Hyun, S., Yu, J., and Shin, C. (2016). An amphiphilic peptide induces apoptosis through the miR29b-p53 pathway in cancer cells. Mol. Ther. Nucleic Acids *5*, e330.

67. Tan, X.L., Moyer, A.M., Fridley, B.L., Schaid, D.J., Niu, N., Batzler, A.J., Jenkins, G.D., Abo, R.P., Li, L., Cunningham, J.M., et al. (2011). Genetic variation predicting cisplatin cytotoxicity associated with overall survival in lung cancer patients receiving platinum-based chemotherapy. Clin. Cancer Res. *17*, 5801–5811.

68. Chen, Q.Y., Jiao, D.M., Wang, J., Hu, H., Tang, X., Chen, J., Mou, H., and Lu, W. (2016). miR-206 regulates cisplatin resistance and EMT in human lung adenocarcinoma cells partly by targeting MET. Oncotarget *7*, 24510–24526.

69. Espana-Serrano, L., and Chougule, M.B. (2016). Enhanced anticancer activity of PF-04691502, a dual PI3K/mTOR inhibitor, in combination with VEGF siRNA against non-small-cell lung cancer. Mol. Ther. Nucleic Acids *5*, e384.

70. Yanagi, T., Tachikawa, K., Wilkie-Grantham, R., Hishiki, A., Nagai, K., Toyonaga, E., Chivukula, P., and Matsuzawa, S. (2016). Lipid nanoparticle-mediated siRNA transfer against PCTAIRE1/PCTK1/Cdk16 inhibits in vivo cancer growth. Mol. Ther. Nucleic Acids *5*, e327.

71. Danesi, R., Altavilla, G., Giovannetti, E., and Rosell, R. (2009). Pharmacogenomics of gemcitabine in non-small-cell lung cancer and other solid tumors. Pharmacogenomics *10*, 69–80.

72. Liu, G., Li, Y.I., and Gao, X. (2016). Overexpression of microRNA-133b sensitizes non-small cell lung cancer cells to irradiation through the inhibition of glycolysis. Oncol. Lett. *11*, 2903–2908.

73. Wu, Y., Crawford, M., Yu, B., Mao, Y., Nana-Sinkam, S.P., and Lee, L.J. (2011). MicroRNA delivery by cationic lipoplexes for lung cancer therapy. Mol. Pharm. *8*, 1381–1389.

74. Naemura, M., Murasaki, C., Inoue, Y., Okamoto, H., and Kotake, Y. (2015). Long noncoding RNA ANRIL regulates proliferation of non-small cell lung cancer and cervical cancer cells. Anticancer Res. *35*, 5377–5382.

75. Sun, C.C., Li, S.J., Li, G., Hua, R.X., Zhou, X.H., and Li, D.J. (2016). Long intergenic noncoding RNA 00511 acts as an oncogene in non-small-cell lung cancer by binding to EZH2 and suppressing p57. Mol. Ther. Nucleic Acids *5*, e385.

76. Sun, C., Li, S., Zhang, F., Xi, Y., Wang, L., Bi, Y., and Li, D. (2016). Long non-coding RNA NEAT1 promotes non-small cell lung cancer progression through regulation of miR-377-3p-E2F3 pathway. Oncotarget *7*, 51784–51814.

77. Meng, Q., Ren, M., Li, Y., and Song, X. (2016). LncRNA-RMRP acts as an oncogene in lung cancer. PLoS ONE *11*, e0164845.

78. Cui, Y., Xie, S., Luan, J., Zhou, X., and Han, J. (2013). Quantitative proteomics and protein network analysis of A549 lung cancer cells affected by miR-206. Biosci. Trends *7*, 259–263.

79. Akopyan, G., and Bonavida, B. (2006). Understanding tobacco smoke carcinogen NNK and lung tumorigenesis. Int. J. Oncol. *29*, 745–752.

80. Wu, J., Yang, T., Li, X., Yang, Q., Liu, R., Huang, J., Li, Y., Yang, C., and Jiang, Y. (2013). Alteration of serum miR-206 and miR-133b is associated with lung carcinogenesis induced by 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone. Toxicol. Appl. Pharmacol. *267*, 238–246.

81. Navon, R., Wang, H., Steinfeld, I., Tsalenko, A., Ben-Dor, A., and Yakhini, Z. (2009). Novel rank-based statistical methods reveal microRNAs with differential expression in multiple cancer types. PLoS ONE *4*, e8003.