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REVIEW

MicroRNAs in lung cancer

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Abstract

MicroRNAs have become recognized as key players in the development of cancer. They are a family of small non-coding RNAs that can negatively regulate the expression of cancer-related genes by sequence-selective targeting of mRNAs, leading to either mRNA degradation or translational repression. Lung cancer is the leading cause of cancer-related death worldwide with a substantially low survival rate. MicroRNAs have been confirmed to play roles in lung cancer development, epithelial-mesenchymal transition and response to therapy. They are also being studied for their future use as diagnostic and prognostic biomarkers and as potential therapeutic targets. In this review we focus on the role of dysregulated microRNA expression in lung tumorigenesis. We also discuss the role of microRNAs in therapeutic resistance and as biomarkers. We further look into the progress made and challenges remaining in using microRNAs for therapy in lung cancer.

Key words: Lung cancer; MicroRNA; MiRNA

Core tip: Lung cancer is a prolific and high mortality disease, with few effective treatments. MicroRNAs have a role in the biogenesis and maintenance of lung cancer, with oncogenic and tumor suppressive effects. They are also a significant factor in resistance to current forms of therapy. There is evidence that microRNAs will be useful as diagnostic and predictive biomarkers in the future and, if delivery challenges can be overcome, they may become integrated into treatments.

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INTRODUCTION

MicroRNAs (miRNAs) are small (19-22 nucleotides) non-coding RNAs that were first discovered in *Caenorhabditis elegans*[1]. MiRNAs silence their target genes by binding to the 3' untranslated region (3'-UTR) of target messenger RNAs (mRNAs), causing either degradation or inhibition of translation. In animals, miRNAs are part of an approximately 70-100 nucleotides RNA with a stem-loop structure, known as a pre-miRNA that is included in hundreds or thousands of nucleotides long primary miRNA precursors (pri-miRNAs). The first step of microRNA biogenesis involves the transcription of the pri-miRNA and this is mediated by RNA polymerase Ⅱ (Pol-Ⅱ)[2], although a minor group of microRNAs can be transcribed by RNA polymerase Ⅲ (Pol-Ⅲ)[3]. Then the pri-miRNA is processed in the nucleus by the RNase Ⅲ enzyme Drosha and the protein Pasha/DGCR8 into pre-miRNAs[4]. The pre-miRNA undergoes a second processing step within the cytoplasm, and a small double-stranded RNA struc-

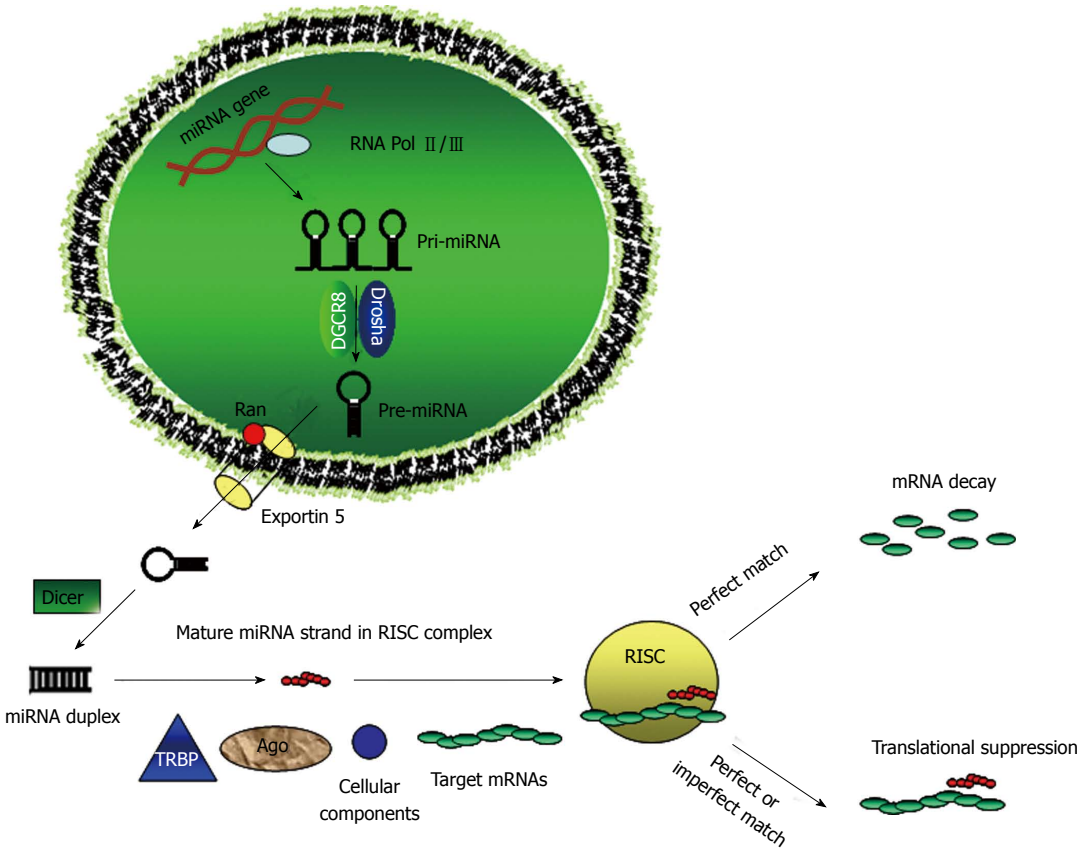

Figure 1 MicroRNA biogenesis. RISC: RNA-induced silencing complex; TRBP: HIV-1 transactivating response RNA-binding protein.

ture approximately 22 nucleotides in length is excised from the pre-miRNA hairpin by another RNase Ⅲ enzyme, Dicer[5,6]. Finally, the mature single-stranded microRNA is loaded into the RNA-induced silencing complex, which mediates the degradation or translation inhibition of target mRNA by binding to its seed sequence in the target mRNA's 3'-UTR (Figure 1). Dysfunctional microRNAs are commonly found in a variety of solid cancers and are attractive candidates for next-generation therapeutics.

Lung cancer remains the leading cause of cancer-related death worldwide, and non-small cell lung cancer (NSCLC) accounts for approximately 80% of all cases[7,8]. Although novel therapies targeting early diagnosis have been developed, the 5-year survival rate for NSCLC patients remains at a low 15%[9]. Takamizawa *et al*[10] were the first to relate microRNA expression to lung cancer. Since then there have been large number of studies relating microRNA expression with lung cancer. Here we describe the roles of microRNAs as tumor suppressors and oncogenes and their role in prognosis and diagnosis of lung cancer. Moreover, we discuss the contribution of microRNAs in radioresistance and chemoresistance as well as several therapeutic ventures involving microRNAs in lung cancer.

MICRORNAS AS TUMOR SUPPRESSORS AND ONCOGENES

Numerous studies have reported finding mutation or aberrant expression of microRNAs in lung cancer patients. Investigators have shown that microRNAs whose expression is altered in tumors, may function as a novel class of oncogenes or tumor inhibitor genes. Several microRNAs are dysregulated in lung cancer, target cancer-relevant targets and have been documented to have tumor-suppressing or tumor-promoting activity in *in vitro* and/or *in vivo* models in lung cancer.

TUMOR SUPPRESSOR MICRORNAS

Let-7

Let-7 was the first microRNA found to be dysregulated in lung cancer. Indeed, Takamizawa *et al*[10] reported that let-7 expression levels are frequently reduced in lung cancers both *in vitro* and *in vivo*. Let-7 subsequently was reported to be inversely correlated with RAS protein expression in lung cancer tissues, providing a possible mechanism for let-7 in lung cancer[11]. Kumar *et al*[12] used both inducible and constitutive expression systems to show substantial tumor suppression by let-7g in xenografts and a mouse lung tumor model in a K-Ras dependent manner. Enforced expression of let-7a in A549 cells decreased NIRF (Np95/ICBP90-like RING finger protein) leading to a coordinated increase in $p21^{WAF1}$[13]. NIRF binds with higher affinity to the methylated CpGs of the promoter region through its SRA (SET and RING finger associated) domain and possibly recruits histone deacytylase-1 (HDAC1) through the same domain. This

recruitment of HDAC1 to the methylated promoter regions of some tumor suppressor genes such as $p21^{WAF1}$ can suppress their expression[14]. Recently[15], let-7c was observed to be inversely correlated to and directly target ITGB3 (integrin b3, also known as CD61)[16], and MAP4K3, a member of the MAP4K family[17] in NSCLC tissues. These observations support the assumption that let-7 may act as a tumor suppressor microRNA.

miR-126

MiR-126 overexpression in lung cancer cell lines decreases Crk protein and leads to decreased adhesion, migration and invasion[18]. Crk is an adaptor protein that mediates several intracellular signal pathways[19] that are important in cell growth, motility, differentiation, and adhesion[20]. Liu *et al*[21] used an RNA protection assay to show downregulation of miR-126 in many lung cancer cell lines. MiR-126 overexpression efficiently reduced the expression of vascular endothelial growth factor (VEGF) and inhibited cell proliferation *in vitro* and tumorigenicity *in vivo*. Futhermore, enforced expression of miR-126 impaired NSCLC cell proliferation and tumor growth in xenografts model by targeting PIK3R2 and thus regulating the PI3K-Akt pathway[22], confirming a tumor suppressive role in lung cancer.

miR-145

Introduction of miR-145 was reported to dramatically suppress the c-Myc/eIF4E pathway by targeting c-Myc, which has been demonstrated to be crucial for cell proliferation in NSCLC cells. Cell growth was inhibited and the G_1/S transition was blocked by miR-145 overexpression in A549 and H23 cells[23]. Enforced expression of miR-145 negatively regulated the expression of EGFR and NUDT1[24]. NUDTI (8-oxo-dGTPase) is involved in accumulated mis-incorporation of oxidized 8-oxo-dGTP into DNA that can lead to cell dysfunction and death[25,26]. When miR-145 was overexpressed in A549 cell line there was a reduction in proliferation of $CD133^+$ lung adenocarcinoma-initiating cells and tumorosphere growth capacity. This tumor suppressive effect involved miR-145 targeting of octamer-binding protein 4, a transcription factor of embryonic stem cells[27,28].

miR-200

miR-200c plays a central role in the process of epithelial-mesenchymal transition (EMT) in highly invasive/aggressive NSCLC cells by targeting TCF8 (ZEB1) thus restoring its regulatory target E-cadherin[29,30]. Loss of miR-200c in invasive cells was observed to be a result of hypermethylation of the promoter region[30]. Studies by Yang *et al*[31] reveal a novel Jagged2/miR-200-dependent pathway that mediates lung adenocarcinoma EMT and metastasis in mice. They showed that Jagged2 increased the expression of GATA-binding factors that in turn suppressed members of miR-200 family driving EMT and reciprocally, miR-200 inhibited GATA3 expression reversing EMT. Furthermore, overexpression of miR-200 in murine lung adenocarcinoma cells decreased their growth and metastasis by targeting Flt1/VEGFR1[32] confirming the EMT suppressive function of miR-200.

miR-34

The miR-34 family (miR-34a, -34b and -34c) is directly regulated by p53 and has been reported to induce apoptosis and cell cycle arrest in cancer cells[33,34] and is being studied for its anti-tumorigenic nature. The receptor tyrosine kinase Axl protein induces proliferation, migration and invasion in cancer[35]. Mudduluru *et al*[36,37] found an inverse correlation between Axl and miR-34a in NSCLC cell lines. ZEB1, a transcriptional repressor that promotes metastasis by downregulating microRNAs like the miR-200 family[38], drives prometastic actin cytoskeletal remodeling in NSCLC cells by inhibiting miR-34a expression[39]. Exogenous miR-34 prevented tumor initiation and progression in a therapeutically resistant $Kras^{G12D/+}$; $Trp53^{R172H/+}$ mouse lung cancer model[40]. Studies in our lab have shown that miR-34a and miR-34c overexpression increased TNF-related apoptosis inducing ligand (TRAIL)-induced apoptosis and decreased invasiveness of lung cancer cells by targeting PDGFR-α and PDGFR-β[41].

ONCOGENIC MIRNAS

miR-17-92

The miR-17-92 intronic cluster comprising seven different microRNAs namely miR-17-5p, -17-3p, -18a, -19a, -19b-1, -20a, and -92 was found by Hayashita *et al*[42] in lung cancer, mostly in small cell lung cancer (SCLC). Antisense oligonucleotides against mir-17-5p and miR-20a induced apoptosis in miR-17-92 overexpressing lung cancer cells[43]. Several targets have been studied for the various members of the miR-17-92 family. MiR-17-92 directly targeted hypoxia-inducible factor (HIF)-1A and overexpression of c-Myc led to downregulation of HIF-1A and induction of miR-17-92, suggesting that the induction of miR-17-92 may play a part in c-Myc–mediated repression of HIF-1A[44]. MiR-17-92 counterbalanced the generation of DNA damage in RB-inactivated SCLC cells by reducing γ-H2AX foci[45]. Matrix metalloproteinase (MMP) play an essential role in tumorigenesis by regulating migration and invasion of cells. *In vivo* MMP activity is controlled by the balance between MMPs and inhibitory proteins such as Reversion-inducing Cysteine-rich protein with Kazal motifs (RECK)[46]. STAT3 was shown to upregulate miR-92a thereby repressing RECK *via* post-transcriptional inhibition and thus promoting MMP activity[47]. These studies suggest that miR-17-92 may be an excellent therapeutic target candidate in the treatment of lung cancer.

miR-21

miR-21 has been reported to be overexpressed in nine types of solid tumors including lung[48] as well as in hematological malignancies such as leukemia[49,50] and has great therapeutic potential for lung cancer. Over-expression

Table 1 MicroRNAs in resistance

miRNAs	Target	Drug/ Treatment	R/S	Ref.
miR-9, let-7g	NFκB1	Radiotherapy	S	[66]
miR-34b	BCL2	Radiotherapy	S	[67]
miR-214	N/A; PTEN	Radiotherapy; gefitinib	R	[68,88]
miR-155	FOXO3A; Apaf-1	Radiotherapy; cisplatin	R	[69,78]
miR-210	Stabilizes HIF-1A in normoxia	Radiotherapy	R	[70]
miR-181	N/A	Cisplatin	S	[72]
miR-451	N/A	Cisplatin	S	[73]
miR-98	TP53	Cisplatin	R	[74]
miR-497	BCL2	Multiple drugs	S	[75]
miR-200b	BCL2, XIAP; E2F3	Cisplatin; docetaxel	S	[76,86]
miR-21	PTEN, BCL2	Cisplatin	R	[79]
miR-135a	APC	Paclitaxel	R	[82]
miR-100	Plk1	Docetaxel	S	[85]
miR-337-3p	STAT3, RAP1A	Paclitaxel and docetaxel	S	[87]
miR-221, miR-222	P27kip1	TRAIL	R	[91]
miR-130a	MET	TRAIL	S	[92]
miR-212	PED	TRAIL	S	[93]

R: Resistance; S: Sensitivity; XIAP: X-linked inhibitor of apoptosis protein; STAT3: Signal transducer and activator of transcription 3; RAP1A: Ras-related protein Rap-1A; MET: met proto-oncogene (hepatocyte growth factor receptor); PED: Astrocytic phosphoprotein PEA-15; FOXO3A: Forkhead box O3; N/A: Not available; p27kip1: Cyclin-dependent kinase inhibitor 1B.

of miR-21 enhanced tumorigenesis through inhibition of negative regulators of the Ras/ MEK/ERK pathway and inhibition of apoptosis[51]. MiR-21 was observed to repress phosphatase and tensin homolog (PTEN) and stimulated growth and invasion in NSCLC cell lines[52]. PTEN overexpression mimicked the same effects of anti-miR-21 such as inhibiting migration and invasion in NSCLC cells[53]. MiR-21 was shown to directly target the 3'-UTR of human mutS homolog 2, a core DNA mismatch repair (MMR) protein[54], thus affecting the cell cycle and cell proliferation in NSCLC cell lines[55] further underlining the oncogenic role of miR-21 in lung cancer.

miR-31

MicroRNAs and DNA mismatch repair have been linked to human cancer progression. Human mutL homolog 1 (*hMLH1*) is a core *MMR* gene and reduced expression of hMLH1 can lead to genetic instability in NSCLC[56]. MiR-31-5p was reported to directly target and to be inversely correlated with MLH1 expression in NSCLC cell lines. Knockdown of miR-31-5p increased hMLH1 protein expression and induced a cell cycle arrest at G_2/M phase in NSCLC cells[57]. MiR-31 was overexpressed in malignant lung tissues from humans and targeted the tumor-suppressive genes large tumor suppressor 2 (LATS2) and PP2A regulatory subunit B alpha isoform (PPP2R2A). Engineered knockdown of miR-31 repressed lung cancer cell growth and tumorigenicity in a dose-dependent manner[58]. These findings reveal that miR-31 acts as an oncogenic miRNA in lung cancer by targeting specific tumor suppressors for repression.

miR-221 and -222

Our group has shown that miR-221 and -222 directly targeted PTEN and Tissue inhibitor of metalloproteinase 3 tumor suppressors inducing TRAIL resistance and enhancing cellular migration through the activation of the AKT pathway and MMPs. We observed that MET oncogene activates miR-221/222 through the c-Jun transcription factor[59]. The p53 up-regulated modulator of apoptosis (PUMA) suppresses growth of A549 cells through induction of apoptosis and sensitizes cells to chemotherapeutic agents and irradiation[60]. It was reported that miR-221/222 directly target and co-modulate PUMA expression and knockdown of miR-221/222 in A549 cells inhibited cell proliferation and induced mitochondrial-mediated apoptosis[61]. Thus, targeting miR-221/222 could be an effective strategy for therapy in lung cancer.

MICRORNAS IN RESISTANCE

Radiotherapy, usually in combination with chemotherapy, is routinely used in lung cancer treatment, especially for NSCLC, allowing for better local control of the disease and reduction of metastasis occurrence. Both radiation resistance and chemoresistance is common, preventing successful long-term therapy and contributing to the dismal prognosis. Investigators are constantly trying to develop new effective therapies by studying the mechanisms behind resistance. Aberrant expression of several miRNAs has been correlated with the development and progression of tumors, and the reversal of their expression has been shown to modulate the cancer phenotype, suggesting the potential of miRNAs as targets for anti-cancer drugs. Here we describe the putative role(s) of microRNAs in the development of resistance to therapy (Table 1).

Radiotherapy resistance

When living cells are exposed to ionizing radiation (IR), a series of alterations occurs including transformation, cell cycle distress, mutations, sister-chromatid exchanges, chromosome aberrations, DNA repair, and apoptosis[62,63]. Among the IR-responsive genes, the activation of NFκB1 following genotoxic stress allows DNA damage repair and cell survival[64] and its inhibition can increase sensitivity of cancer cells to chemotherapeutic agents and radiation exposure[65]. Overexpression of miR-9 has been shown to down-regulate the level of NFκB1 in γ-irradiated H1299 human lung cancer cell line and decrease the surviving fraction of γ-irradiated cells. Interestingly, let-7g also suppressed the expression of NFκB1, although there is no canonical target site for let-7g in the NFκB1 3'-UTR[66]. Tumor suppressor p53 is another key player of the complex DNA damage response activated in response to IR[63]. Overexpression of p53-regulated miR-34b[33,34] in p53 wild type A549 cells increased radiosensitivity at low doses of radiation and this effect was not observed in p53 null H1299 cells[67].

Several microRNAs are involved in inducing resistance to irradiation. MiR-214 was shown to be upregulated

in radioresistant NSCLC cells relative to radiosensitive counterparts and its overexpression protected radiosensitive cells against RT-induced apoptosis[68]. Incubation of NSCLC cell lines in hypoxic environments was reported to induce miR-155 expression and decrease its target, FOXO3A, a tumor suppressive transcription factor that regulates cell cycle and apoptosis. These increased levels of miR-155 radioprotected lung cancer cells and vice versa[69]. In another study, enforced expression of miR-210 increased radioresistance of NSCLC cells by stabilizing HIF-1A[70]. These studies reveal a therapeutically important link between miRNA expression, hypoxia, and irradiation.

Chemotherapy resistance

Platinum agents like cisplatin and carboplatin are some of the principal chemotherapeutic agents used for treatment of NSCLC. These agents induce their cytotoxic effects by targeting cellular DNA and are active against a number of tumour types[71]. However numerous studies have shown that an initial success associated with partial responses or disease stabilization is followed by the selection of chemotherapy-resistant tumor cells, leading to chemotherapeutic failure. Numerous microRNAs have been implicated in cisplatin resistance. Galluzi and colleagues reported miR-181a and miR-630 to be the most upregulated miRNAs after cisplatin (CDDP) treatment however, pre-miR-181a enhanced while pre-miR-630 reduced CDDP-triggered cell death in A549 cells by modulating steps of the intrinsic pathway of apoptosis[72]. Another group observed that ectopic expression of miR-451 might be involved in sensitizing A549 cells to cisplatin by inducing apoptosis *via* inactivation of Akt signaling pathway and enhancement of caspase-3 activity[73]. Zhang *et al*[74] showed that transfection with miR-98/miR-453 inhibited p53 expression and upon treatment with cisplatin, the expression of miR-98 decreases, while p53 increases. This led them to speculate that regulation of p53 pathway might play an important role in the action of cisplatin on A549 cell growth. Separate studies by Zhu *et al*[75,76] on miR-497 and miR-200b/429 cluster in multidrug resistant A549/CDDP cell line indicated an increased sensitivity to cisplatin in part by modulation of apoptosis *via* targeting only B-cell CLL/lymphoma 2 (BCL2) or both BCL2 and X-linked inhibitor of apoptosis, respectively. In the cytosol, Apaf-1 can bind with cytochrome-c released from the mitochondrial inter-membrane, and activate the initiator caspase-9, eventually resulting in cellular apoptosis[77]. MiR-155 was observed to be inversely correlated to Apaf-1 in lung cancer tissues. Silencing miR-155 or overexpressing Apaf-1 in A549 cell lines greatly increased the sensitivity of A549 cells to cisplatin treatment through an Apaf-1 mediated pathway, involving increased expression of Bax and caspase-9[78]. MiR-21 was reported to be critical in platinum resistance in NSCLC and modulated the sensitivity of NSCLC cells to platinum, at least in part, by regulating PTEN and BCL-2 expressions[79].

Taxanes, such as paclitaxel and docetaxel, are chemotherapeutic drugs that stabilize microtubules and inhibit their disassembly to tubulin interfering with proper formation of the mitotic spindle, which leads to activation of the mitotic spindle checkpoint and mitotic arrest[80]. Drug-treated cells then undergo apoptosis as a result of the abnormal mitosis[81]. Studies reporting the role of microRNAs in taxane resistance can provide novel adjuvant strategies along with taxanes in the treatment of lung cancer. Knockdown of miR-135a was reported to upregulate adenomatous polyposis coli gene (*APC*) and sensitize paclitaxel-resistant NSCLC cell lines to paclitaxel-induced cell death[82]. APC is a tumor suppressor that regulates the mitotic checkpoint by binding to microtubules during mitosis[83]. Polo-like kinase (Plk)-1 is a cell cycle protein that plays an important role in spindle dynamics and chromosome segregation during mitosis[84]. Feng *et al*[85] showed that introduction of miR-100 resensitized docetaxel resistant SPC-A1/DTX cells to docetaxel by suppression of cell proliferation, enhancement of apoptosis, and cell arrest in G_2/M phase of cell cycle at least partially by Plk-1 targeting. The same group also reported that ectopic expression of miR-200b reversed docetaxel resistance of SPC-A1/DTX cells in part by targeting E2F3[86]. Du and colleagues identified a novel regulatory pathway involving STAT3 and RAP1A that modulates miR-337-3p mediated paclitaxel sensitivity in lung cancer cells[87].

Patients with NSCLC who have activating epidermal growth factor receptor (EGFR) mutations derive clinical benefit from treatment with EGFR-tyrosine kinase inhibitors (EGFR-TKIs)-namely gefitinib and erlotinib. However, these patients eventually develop resistance to EGFR-TKIs. Wang *et al*[88] established a gefitinib resistant cell line-HCC827/GR and found that miR-214 was significantly up-regulated in these cells compared to control HCC827 cells. Knockdown of miR-214 in HCC827/GR resulted in upregulation of PTEN and inactivation of p-AKT and this in turn re-sensitized the cells to gefitinib. To understand the role of microRNAs in TKI-resistant NSCLCs, our group examined miRNA dysregulation mediated by TK receptors. MiR-30b, -30c, -221 and -222 were found to be modulated by both EGFR and MET receptors whereas miR-103 and miR-203 were controlled only by MET. We showed that these miRNAs influenced the response to gefitinib of NSCLC cells *in vitro* and *in vivo* by inhibiting the expression of the genes encoding BCL2-like 11 (BIM), apoptotic peptidase activating factor 1 (APAF-1), protein kinase Cε (PKC-ε) and sarcoma viral oncogene homolog[89].

Treatment with TRAIL induces programmed cell death in a wide range of transformed cells, both *in vitro* and *in vivo*, without producing significant effects in normal cells[90]. However, a significant proportion of human cancer cells are resistant to TRAIL-induced apoptosis, and the mechanisms of sensitization vary among cell types. To define novel pathways that regulate TRAIL-sensitivity in NSCLC, our lab performed genome-wide expression profiling of microRNAs. Levels of miR-221 and -222 were increased in TRAIL-resistant NSCLC cells and their knockdown rendered CALU-1-resistant cells sensitive to TRAIL. Conversely, H460-sensitive cells

Table 2 MicroRNA in diagnosis and prognosis. Traditional methods of diagnosing and evaluating lung cancer and their corresponding potential microRNA biomarkers

	Traditional Procedures	Possible microRNA biomarkers
Diagnosis		
Detect abnormalities	X-ray, CT scan	21
Confirm malignancy	Biopsy, sputum/fluid cytology	let-7, 29a, 34c, 205, 375
Prognosis		
Staging	CT scan, PET, MRI	21, 125b, 155, 182/183
Mutational status	Sequencing, PCR, microarray	21, 155

CT: Computed tomography; PET: Positron emission tomography; PCR: Polymerase chain reaction; MRI: Magnetic resonance imaging.

treated with pre-miR-221 and -222 developed a resistance. Interference with TRAIL signaling by miR-221 and -222 was mainly through targeting p27kip1[91]. Another study from our lab further reported that miR-130a, expressed at low level in lung cancer cell lines, by targeting MET was able to reduce TRAIL resistance in NSCLC cells through the c-Jun-mediated downregulation of miR-221 and miR-222[92]. Ectopic expression of miR-212 increased TRAIL-induced cell death in NSCLC cells by targeting PED/PEA-15 (PED), a death effector domain family member with a broad anti-apoptotic function[93]. These studies enhance our understanding of the mechanisms responsible for TRAIL resistance.

MIRNAS IN DIAGNOSIS

The diagnosis of lung cancer is performed through several methods with varying degrees of sensitivity and reliability. X-ray imaging, along with positron emission tomography and computed tomography (CT) scans, is often the first diagnostic procedure utilized. While these methods provide valuable information when anomalies are easily visible, problems with lung segmentation and positioning in the chest cavity, human error and competent detection software prevent imaging from always producing successful diagnoses. Similarly, while tissue sampling though bronchoscopy has become the standard practice in diagnosing lung cancer, it presents its own difficulties, including complications in obtaining viable samples due to patient symptoms, proper imaging and tumor position[94].

MicroRNAs show potential as biomarkers for the diagnosis of lung cancer that can complement and improve upon other techniques. Promising lung cancer microRNA biomarkers can be found circulating in the bloodstream, in sputum and inside cells, and are detected at an abnormal level when cancer is present. Ideally, these biomarkers should be detected through minimally invasive methods and with limited discomfort to patients. There are currently several dozen microRNAs under investigation for their biomarker properties (Tables 2 and 3).

MiR-21 has a well-documented correlation to lung cancer. Detected in both serum and sputum, elevated miR-21 corresponds to lowered survival rate, lymphoid invasions and KRAS mutations[53,95]. Promisingly, assays for miR-21 in sputum from lung cancer patients have shown higher sensitivity than traditional sputum cytology with very high specificity[96,97]. MiR-21, in combination with miR-210 and miR-486-5p, was shown to be expressed significantly higher in the plasma of patients with malignant solitary pulmonary nodules (SPNs) compared to those with benign SPNs. Solitary pulmonary nodules have been increasingly diagnosed with the improvement of CT scan technology and its widespread use. However, only a small fraction of SPNs are malignant. The combination of miR-21 testing and CT scans could provide a minimally invasive method of determining the cancer status of patients with SPNs[98].

Table 3 MicroRNAs with potential relevance to common types of lung cancer treatment

Treatment	Potential prognostic biomarkers	Potential role in resistance
Surgery	Let-7, 21	
Radiotherapy	155, 210	Let-7g, 9, 34, 155, 210, 214
Chemotherapy	21, 125b	21, 30b/c, 98, 100, 103, 130a, 135a, 155, 181, 200b, 203, 212, 214, 221/222, 337, 451, 453, 494, 630

MiR-155 is a prominent oncomiR, with various roles in lung cancer including proliferation and drug resistance. Used in a panel with miR-197 and miR-182, miR-155 was able to distinguish between NSCLC patients and control samples by real time PCR of plasma. Patients with metastasizing cancer consistently exhibited higher levels of plasma miR-155, which could additionally aid in staging the disease[99]. Several studies have found that miR-155 is only elevated in EGFR/KRAS-negative lung cancer. Samples from surgically resected lung specimens and fine needle aspirations (FNAs) both demonstrated this effect[100,101]. FNAs are considered to be safe, minor surgical procedures compared to excisional biopsies, thus further development of its use for collection of miR-155 to determine mutational status could be beneficial. An even less invasive technique was used by Yao and colleagues to determine levels of miR-155 *in vivo*[102]. They developed a novel molecular beacon that can be introduced into mice with lipid-DNA complexes and detect miR-155 in lung cancer xenografts through *in vivo* fluorescent imaging. The authors posit that these results may be translatable to human lung tumors, possibly improving on the problematic imaging resources currently available for diagnostics.

The miR-183 family (miR-96, miR-182, and miR-183) is a group of oncomiRs that have been confirmed to be overexpressed in lung tumors and serum in NSCLC. Targets for these miRs support a variety of biological processes, including growth, migration, invasion and angiogenesis. MiR-182 in particular has been found to be strongly correlated to primary tumors while all three are expressed more in squamous cell carcinoma than in ad-

enocarcinoma[103-105]. Additionally, miR-182 showed a high specificity and sensitivity, and readily differentiates stage I lung cancer from normal control samples, making it a tantalizing possibility for non-invasive clinical diagnostics. MiR-183, on the other hand, has been demonstrated as being able to differentiate between early and late stage NSCLC, while not being able to discriminate early stage lung cancer from normal cells[106].

The miR-34 family, in particular miR-34a and miR-34c, has been shown by multiple groups to be potential biomarkers in lung cancer[100]. Mascaux and colleagues detailed an inverse relationship between miR-34 levels and lung carcinogenesis, and later expounded on this by showing that changes in lung cell histology are reflected by miR-34c independent of any treatment[107]. However, these studies used biopsies as their source tissue, and have not yet confirmed that other extraction methods (sputum, serum, *etc*.) could be used to circumvent normal tissue sampling and histology. Akbas *et al*[108] have found that dysregulation of 34c can be confirmed through serum in chronic obstructive pulmonary disease (COPD) - an inflammatory disease that increases the risk of lung cancer - making further development of 34c as a lung cancer biomarker a likely avenue of research.

NSCLC is the most common form of lung cancer, and is divided into two subtypes, squamous cell carcinoma (SCC) and adenocarcinoma. Diagnosing the correct subtype is critical for treatment and microRNA biomarkers that are able to distinguish between these subtypes would be a useful tool in a clinical setting. MiR-205 - a tumor suppressor - has been found by several researchers to be a highly effective identifier of squamous cell histology through its downregulation, both in NSCLC tissues and serum[109,110]. Similarly, members of the let-7 family are significantly downregulated in SCC, likely due to the fact that let-7 regulates RAS expression, and RAS mutations are far more common in SCC than adenocarcinomas[111,112]. As lung tissue has one of the highest expressions of let-7 in the body, its characteristic decrease in SCC has the potential to make it an easily identifiable biomarker[113]. However, because this large decrease in expression has only been identified in lung tissue and not sputum, serum or bronchial fluids, the only current options for assaying let-7 are tissue biopsy or bronchial brushing. Thus, let-7 as a biomarker will have to show greater efficacy than traditional cytopathology to warrant clinical use.

Though less common and with comparatively little research, small cell lung cancer presents serious problems for patients, with a tendency toward rapid and widespread metastasis. Therefore, accurate and expeditious diagnostic markers are desirable. Two studies have found miR-375 to accurately discriminate between NSCLC and SCLC. Huang *et al*[114] used snap-frozen and paraffin-embedded surgical lung specimens, finding miR-29a and miR-375 to be superior to traditional cytopathology for diagnosing SCLC. In the other study, Zhao and colleagues found extremely elevated miR-375 expression in four human SCLC cell lines and four SCLC-like cell lines generated in mice[115]. These results are promising, but require more study with larger sample populations and examinations of extracellular microRNA levels to evaluate the usefulness of miR-375 as a clinical biomarker.

MIRNAS IN PROGNOSIS

An essential facet of cancer treatment involves the correct and efficient prognosis of the type of cancer and the expectations of survival and mortality. This prevents the unneeded use of potentially harmful drugs, and allows for the correct prescription of treatment strength and severity. As microRNAs have been confirmed to play roles in lung cancer development, migration and response to therapy, they may also find future use as biomarkers to give accurate prognoses to physicians.

Liu *et al*[116] found that miR-21 was significantly elevated in the serum of NSCLC patients with lower survival rates and showed a strong association with lymph node metastasis and advanced clinical stage. Yang *et al*[117] confirmed this result with a meta-analysis while others found similar results in three ethnically-diverse cohorts, including significant associations between elevated miR-21 and high-mortality stage I tumors[118,119]. These findings have the potential of allowing physicians to quickly evaluate and escalate treatments in response to early stage NSCLC diagnoses. Studies examining post-operative lung cancer patients also found that miR-21 serum levels significantly decreased in response to successful surgery, with higher miR-21 expression corresponding to shorter survival time and disease recurrence[120]. However, another study evaluating the use of miR-21 as a predictive biomarker in SCLC found no correlation between miR-21 expression and patient outcome[121]. The same study found similar results with 6 other important NSCLC-related miRs, underlying both the inherent differences between SCLC and NSCLC and also the paucity of data involving SCLC biomarkers. MiR-155 has been shown to have a similar elevation in expression in NSCLC, which is associated with low survival and high rates of recurrence[122,123]. Both miR-21 and miR-155 have been examined in sputum samples and found in readily detectable quantities, and while Xie and collaborators found only miR-21 produces adequate differentiation in expression for use as a biomarker[97], others have found using both in combination with three other miRs to be a highly sensitive panel for clinical applications[124].

The let-7 family, in addition to discriminating between SCC and adenocarcinoma, has also been found to be associated with survival rate. Low let-7a expression has been shown by multiple studies to correlate to a poor prognosis, both pre- and post-operative, particularly in SCC[125]. There is some evidence that this preferential prognostic ability comes from the squamous cell carcinoma's reliance on the downregulation of tumor suppressor miRs, including let-7, compared to adeocarcimoma's dependence on the upregulation of oncomiRs[111].

Several miRs have been identified as having the potential to predict the effectiveness of therapy. MiR-125b is an oncomiR that has been found to be significantly increased in stage Ⅲ and Ⅳ NSCLC. Cui *et al*[126] examined the expression of a panel of miRs, finding that miR-125b levels were markedly higher in patients that did not respond to cisplatin treatment. This corroborates several other studies that found that miR-125b inhibited cisplatin-induced apoptosis in breast and ovarian cancers[127,128]. Similarly, miR-21 shows promise as predictive biomarker for the response to adjuvant platinum based chemotherapies (cisplatin, oxaliplatin, *etc*.) in NSCLC[79]. Serum taken from patients after surgery and platinum based treatment showed elevated levels of miR-21 compared to a pre-treatment baseline if there was a low chemotherapeutic response. A recent study found that serum miR-210 consistently determined the success of platinum based chemotherapy. MiR-210 is upregulated in NSCLC and recent findings have shown that patients who responded well to treatment had significantly lower expression of miR-210 in serum, near levels expected in healthy control subjects[129]. Another study reported that NSCLC cells overexpressing miR-210 were conferred with radioresistance as well, displaying an ability to rapidly repair double-strand DNA breaks[70]. As radiotherapy is a common treatment in lung cancer, with more than half of patients receiving irradiation, potential microRNA biomarkers - miR-210 for example - that predict the efficacy of this procedure would make an immediate impact on patients and physicians' decisions. In its role as a mediator of radioresistance, miR-155 may also have potential as a prognostic biomarker, with elevated expression corresponding to lower survival rate in patients who have received radiotherapy[69,130].

MIRNAS AS POTENTIAL TREATMENTS

Increasing evidence supporting the essential role of microRNAs in the machinery of cancer points to the possibility of using microRNAs as treatments in lung cancer. The most evident problem blocking clinical use of microRNA therapies is delivery. Specifically targeting cancer cells, maintaining microRNA stability in bodily fluids and penetration of cellular membranes are areas of intense investigation. Some modifications to microRNA and anti-microRNA oligonucleotides (AMOs), including 2'-O-methyl, 2'-O-methoxyethyl and locked nucleic acids, provide nuclease resistance for greater longevity during serum transport, but additional methods are needed to enhance the cell permeability of these molecules[131].

Liposomes are a promising avenue of microRNA therapy delivery. These artificial, spherical vesicles made from a lipid bilayer are used to administer pharmaceutical drugs, microRNA or small interfering RNA (siRNA). Experiments using mouse models have found both neutral lipid emulsions and cationic lipoplexes to be effective in delivering microRNAs to lung tumors. Multiple studies have used a neutral lipid emulsion to deliver tumor suppressors miR-34a and let-7 to NSCLC tumors in mice, which resulted in a 60% reduction in tumor area[132,133]. Wu and colleagues found that cationic lipoplexes were over 50-fold more effective in delivering pre-miR-133b, a known inhibitor of NSCLC proliferation, to NSCLC mice than NeoFX complexes, a standard transfection reagent, and with lower cytotoxicity[134,135]. Recently, this same team used cationic lipoplexes to deliver miR-29b into murine A549 xenografts, finding similar success in cellular penetration, along with documenting a decrease in tumorigenicity and improved functionality of cisplatin[136]. Shi and colleagues have used a novel technology - solid lipid nanoparticles (SLNs) - to transport AMOs to suppress miR-21 in lung cancer and introduce miR-34a into lung cancer stem cells, inhibiting cell migration and inducing cell apoptosis[137]. SLNs boast superior cellular uptake rates and decreased oligonucleotide degradation, which allow AMOs to be introduced without stability-adding modifications that reduce specificity. Future directions for liposome therapy reseach include increasing stability of liposomes and better targeting through the use of tumor-recognizing antibodies and peptides. Some studies have already shown that incorporating ligands that target overexpressed lung cancer receptors into liposomes dramatically improves liposome uptake into NSCLC cells[138] while others have used synthetic antigens to activate tumor-targeting immune cells[139].

Viral delivery systems are a platform that offers naturally high infection rates and high miRNA expression levels for lung cancer treatment. Adenoviruses have been used as a vector for the delivery of miR-122, a tumor suppressor, into NSCLC NCI-H460 cells. The resulting 2000-fold higher expression of miR-122 led to the activation of intrinsic apoptotic pathways[140]. Sun and colleagues used a lentiviral vector to infect hepatocellular carcinoma cells with osteopontin-suppressing microRNAs that decreased tumorigenicity in mice and down-regulated the oncogenic MEK/ERK/1/2 pathway[141]. These results may be transferable to lung cancer, as osteopontin has been identified as a pro-metastatic factor in NSCLC[142]. Overall, adenoviruses are considered the better option for microRNA vectors as they do not integrate into the genome. There are complications with viral delivery of microRNAs, though, including immunogenicity and cellular toxicity that will need to be addressed in further research.

As liposome delivery often produces toxicity and requires considerable optimization to maintain adequate stability and efficacy, and viral vectors are limited by immunogenicity much research has recently focused on the use of nanoparticles. These small, solid spheres offer reduced immune response, lower toxicity and cheap, efficient production methods that result in high complex stability.

Protamine, a biologically derived molecule, has been complexed with microRNA, resulting in higher transfection rates than with lipoplexes[143]. Chen *et al*[144] utilized protamine complexes with miR-34a to inhibit the growth of lung metastases of melanoma. These nanoparticles incorporated a liposome shell around the nanoparticles,

with great effectiveness. Further studies are needed to determine the necessity of liposomal encirclement of protamine complexes, taking into account microRNA degradation, cellular uptake and immune response. Gold and silica nanoparticles have also been utilized in microRNA delivery[145,146], but as of yet, there are no studies demonstrating their use in treating lung cancer.

CONCLUSION

MiRNAs have become recognized as key players in cancer. Their ability to regulate expression of cancer-related genes has immense implications for the diagnosis and treatment of cancer. Lung cancer is the leading cause of cancer-related death worldwide and currently has a substantially lower survival rate than many other common cancers. In this review, we discuss how dysregulated miRNA expression has been shown to contribute to the genesis and maintenance of lung cancer, through the down-regulation of tumor suppressors and up-regulation of oncomiRs. Additionally, miRNAs may be essential in the development of chemo- and radioresistance in lung cancer. Due to their importance in the regulatory structure of cancer, miRNAs may soon be used to improve diagnosis and predictions of outcomes and response to therapy, although more studies will be needed with larger sample groups to resolve conflicting reports of disease-state expression patterns for some miRNAs. Implementing miRNAs and anti-miRNAs as treatments presents some additional difficulties, mostly related to delivery and stability inside the body, but holds promise as a less toxic therapy that can target multiple genes simultaneously. The investigation into miRNAs and cancer is still relatively new, and more study will be needed to form consensuses on the critical functions of miRNAs inside cancer cells, what information can be gleaned from changes in their expression and the best methods for therapeutic administration, but these unique compounds show great promise as tools against lung cancer.

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