

# MicroRNA-126: A new and promising player in lung cancer (Review)

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**Abstract.** Lung cancer is one of the most common malignant tumors associated with cancer death; however, the mechanisms involved in lung tumor development have not been completely elucidated, which impedes the advancement of clinical diagnosis and therapy. MicroRNA-126 (miR-126) is an important member of the microRNA family and is encoded by intron 7 of epidermal growth factor-like domain-containing gene 7. Increasing evidence has demonstrated that miR-126, as a distinct endothelial-enriched miRNA and new tumor suppressor gene, serves a promising role in the occurrence, development and metastasis of various types of cancer, including liver cancer, colorectal cancer, melanoma and lung cancer. In the present review, the current knowledge of the role of miR-126 in lung cancer growth, metastasis, diagnosis and prognosis as well as therapy was summarized, which may provide new insights on the biological roles of miRNAs in lung cancer and facilitate the

ultimate development of miRNA-based therapies in clinical patients with non-small cell lung cancer.

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## 1. Introduction

Lung cancer is the leading cause of cancer mortality worldwide, and >1 million people die of this disease each year since 2006 (1). However, the complicated mechanisms involved in tumor development have not been completely elucidated, which impedes the development of early lung cancer diagnosis and therapy (2,3). Hence, to develop effective clinical therapies against lung cancer, it is extremely urgent that the potential molecular mechanism of lung cancer development be further explored. Previous studies have discovered that a class of small non-coding RNAs, namely microRNAs (miRNAs), serve as intermediate regulators of cellular biological functions such as cell development, growth and apoptosis, which has opened up a whole field of genomics called microRNomics (4,5). Importantly, numerous studies have shown that miRNAs play critical roles in the development and metastasis of lung cancer, and miRNAs have emerged as potential factors in the early diagnosis and prognosis of lung cancer.

MicroRNA-126 (miRNA-126, miR-126) is an important member of the miRNA family, encoded by intron 7 of epidermal growth factor-like domain-containing gene 7 (*EGFL7*) on human chromosome 9q34.3 (6,7). Three *EGFL7* isoforms (named *EGFL7* isoform A, B and C), all of which contain the same open reading frame but are transcribed from separate promoters, utilize alternative exons (Fig. 1). At the transcriptional level, miR-126 may silence genes such as *mTOR*, *PIK3R2*, and indirectly regulate *EGFL7* isoform B (8-10). Currently, miR-126 has been reported to have

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*Abbreviations:* AKT, protein kinase B; AUC, area under the curve; CI, confidence interval; Crk, v-crk sarcoma virus CT10 oncogene homologue; *EGFL7*, epidermal growth factor-like domain-containing gene 7; EMT, epithelial-mesenchymal transition; ERK, extracellular protein kinase; HR, hazard ratio; lncRNA-PVT1-5, long non-coding RNA-PVT1-5; MAPK, MAP kinase; miRNAs, microRNAs; miR-126, microRNA-126/miRNA-126; MVD, microvessel density; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; PI3K, phosphatidylinositol-3 protein kinase; PTEN, phosphatase and tensin homologue; *SLC7A5*, solute carrier family 7 (cationic amino acid transporter, y+ system) member 5; TBMS1, tubeimoside-1; TFs, transcription factors; Tregs, regulatory T cells; VEGF-A, vascular endothelial growth factor A; VEGF, vascular endothelial growth factor; VEGFR-2, vascular endothelial growth factor receptor-2

*Key words:* lung cancer, microRNA-126, therapy, growth, metastasis

altered expression in various cancer tissues, including liver, colorectal cancer and melanoma as well as lung cancer, and it has been well studied for its role in lung cancer tumorigenesis as well as in diagnosis and therapy (2,11-15), indicating the promising role of miR-126 in lung cancer treatment.

## 2. miR-126 and lung cancer tumorigenesis

*miR-126 and cancer cell growth.* Numerous studies have documented that miR-126 can control the growth of lung cancer cells. For instance, miR-126 can mediate the activation of the signal transducer and activator of transcription 3 signaling pathway to regulate the malignant biological behavior of non-small cell lung cancer (NSCLC) cells including their proliferation, migration, cell cycle entry and apoptosis susceptibility (16). In addition, miR-126 can activate the proapoptotic and anti-metastatic effects in lung cancer cells by blocking the vascular endothelial growth factor A (VEGF-A)/vascular endothelial growth factor receptor-2 (VEGFR-2)/extracellular protein kinase (ERK) signaling pathway (17). Recently, Chen *et al* (18) demonstrated that silencing miR-126 could reverse the anti-cancer effects of naringin on NSCLC cell growth, in which naringin induces a reduction in the phosphatidylinositol-3 protein kinase (PI3K)/protein kinase B (AKT)/mechanistic target of rapamycin and suppresses vascular cell adhesion molecule 1 protein levels. In addition, miR-126 exhibits a suppressive effect on NSCLC cell invasion by interacting with three hub genes: VEGFA, AKT1, and Kirsten rat sarcoma viral oncogene homologue (19). Additionally, other studies have demonstrated that miR-126 can suppress the growth, migration and invasion of NSCLC cells by targeting chemokine (C-C motif) receptor 1 and solute carrier family 7 (cationic amino acid transporter, y+ system) member 5 (SLC7A5) or v-crk sarcoma virus CT10 oncogene homologue (Crk) (20-23), indicating that miR-126 may control the growth of lung cancer cells through multiple targets (Table I).

*miR-126 and cancer cell metastasis.* It is universally acknowledged that epithelial-mesenchymal transition (EMT) serves a critical role in lung cancer metastasis (24-26). Studies have demonstrated that miR-126 is a key regulator that controls EMT signaling in lung cancer. For instance, in SPC-A1 lung cancer cells, ectopic expression of miR-126 significantly suppresses the EMT process by directly targeting PI3K/AKT/Snail signaling, which is considered to be the initial step of tumor metastasis (27). Consistently, the upregulation of miR-126 can also inhibit the migratory and invasive abilities of NSCLC cells by decreasing the expression of the target gene *PIK3R2* and influencing the transduction of the phosphatase and tensin homologue (PTEN)/PI3K/AKT signaling pathway (10,28). Further studies have demonstrated that both strands of the miR-126 and the complementary 'passenger strand' of the miR-126 duplex simultaneously target cytokine stromal cell-derived factor-1 $\alpha$  to reduce the recruitment of mesenchymal stem cells and inflammatory monocytes to primary tumors, thereby inhibiting lung metastasis (29). This indicates that miR-126 may regulate metastasis by affecting the tumor microenvironment (29). In addition, miR-126 has been identified in the miRNA-transcription factor (TF) target regulatory network in cancer metastasis (30). Novel differentially

expressed genes including glutamate receptor, metabotropic 8 and dachshund family transcription factor 1 are all regulated by miR-126, which is implicated in the lymph node metastasis process of small cell lung cancer (30). However, the exact role of miR-126 in TF-miR networks, especially the interaction among these different TFs in lung cancer metastasis remains to be elucidated.

*miR-126 and angiogenesis.* Angiogenesis is well known as a representative event in tumorigenesis (31-34). miR-126 is generated from a subset of *Egfl7* transcripts in which intron 7 is retained (35). EGFL7 is a member of the epidermal growth factor-like protein family and is an extracellular matrix-associated protein expressed in activated endothelium (36,37). Studies have reported that miR-126 and *Egfl7* can regulate angiogenesis and maintain vascular integrity through both their interaction and their independent action (35,38-40). Notably, it has been revealed that EGFL7, insulin receptor substrate-1 and Crk are important miR-126 targets in lung cancer tumorigenesis. The aforementioned targets can inhibit tumor growth by modulating tumor angiogenesis (40,41).

In addition, *VEGF-A* serves an important role in the effect of miR-126 in cancer angiogenesis (42,43). VEGF-A is an essential angiogenic growth factor that is a powerful promoter of the adhesion and proliferation of vascular endothelial cells (44,45). Hence, VEGF-A can regulate the development of various cancers including liver cancer, colorectal cancer, melanoma and lung cancer (46-49). MiR-126 can inhibit the expression of sprouty-related EVH1 domain-containing gene 1 (SPRED), an inhibiting factor of the MAP kinase (MAPK) pathway, and the *p3kr2* (PI3KR2/p85-b) gene, a subunit of PI3K (50-52). When miR-126 is downregulated, the overexpression of SPRED and the PI3K regulatory subunit suppresses the MAPK and PI3K signal pathways, which affects the transmission of VEGF-A and leads to further angiogenesis (50-52). Hence, investigating of miR-126 indicates that it may be used as a vascular endothelial cell-specific regulator of angiogenic signaling (35). Similarly, studies have revealed that angiogenesis may be promoted by the downregulation of miR-126 expression, which can lead to increased microvessel density (MVD) in lung cancer tissue (53,54). In addition, MVD and the levels of vascular endothelial growth factor (VEGF) are both reduced dramatically once miR-126 expression is restored, which results in the inhibition of the growth of lung cancer (53).

## miR-126 and lung cancer diagnosis

Recent studies have suggested that miR-126 may serve as an exciting new diagnostic biomarker of lung cancer (Table II). For example, Shang *et al* (55) demonstrated that the specificity and sensitivity of serum miR-126 levels in predicting NSCLC development were 84.3 and 96.40%, respectively. In addition, Yang *et al* (56) demonstrated that the diagnostic performances of miRNAs such as miR-21, miR-223, miR-155 and miR-126 in serum and plasma in lung cancers were good and that serum miRNAs performed better compared with plasma miRNAs, with a sensitivity of 79%, specificity of 78%, positive likelihood ratio of 3.7, diagnostic odds ratio of 14 and area under the curve (AUC) of 85%. Even the diagnostic accuracy of these miRNAs on stage I/II and an additional stage I group was similar to

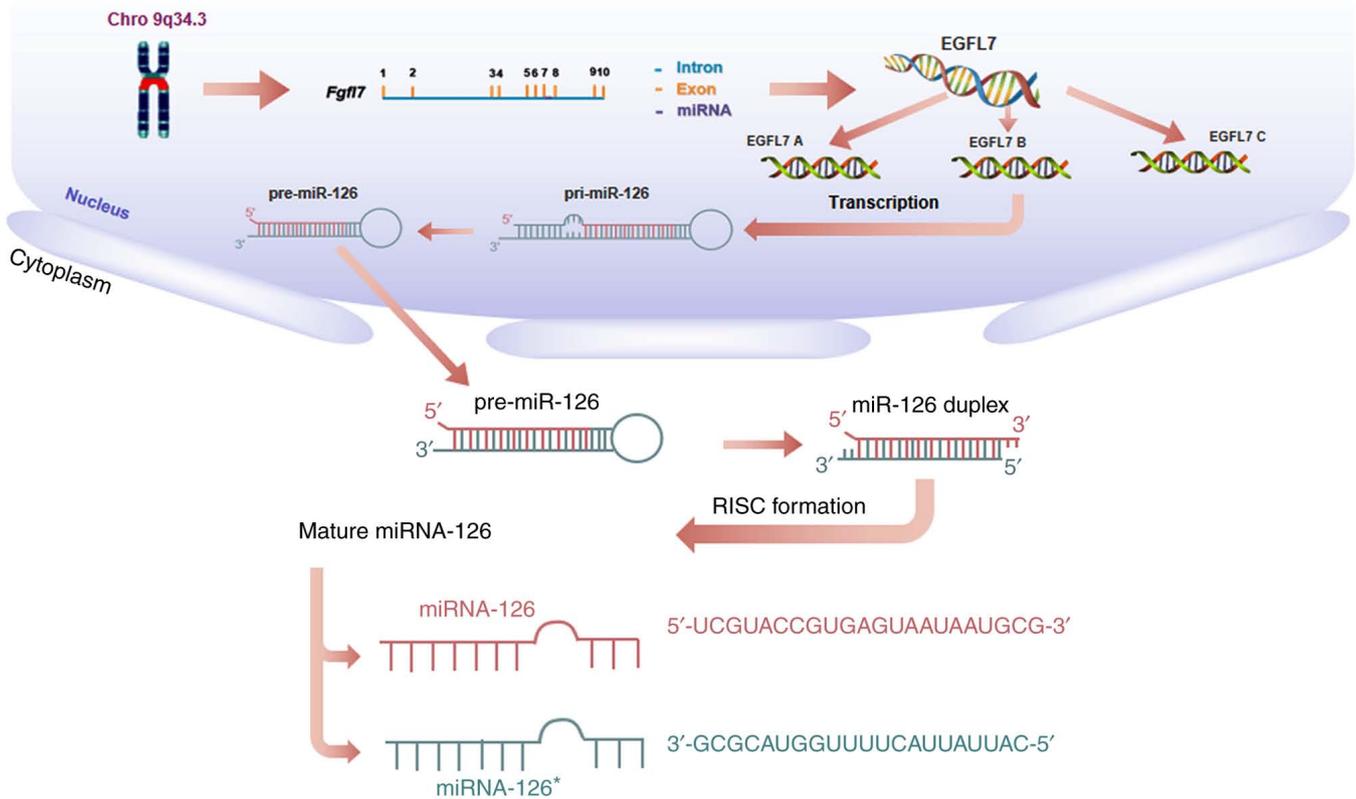


Figure 1. Biogenesis of miR-126. miR-126 is transcribed from the intron of the *Fgf17* genomic locus on chromosome 9q34.3 into primary miR-126 transcripts (pri-miR-126), which are processed into hairpin precursor molecules (pre-miR-126) and then further into the two different mature miRNA sequences [(miR-126, miR-126\* (the complementary 'passenger strand' of miR-126)], which are incorporated into the RISC complex and guided to miR-126 target mRNAs to repress their expression. miR, microRNA; EGF7, epidermal growth factor-like domain-containing gene domain-containing gene 7; RISC, RNA-induced silencing complex; *Fgf17*, epidermal growth factor-like domain-containing gene 7.

that of all-stage lung cancer, which suggests that circulating miRNAs can correctly distinguish every stage of lung cancer from controls correctly (56). In addition, the expression of miR-126 in serum of patients with asbestos-related NSCLC was comparable to that of patients with asbestos-unrelated NSCLC, which may indicate the diagnostic value of miR-126 in asbestos-related NSCLC (57). In contrast, another recent study mentioned that the levels of both serum and serum exosomal miR-126 in the early NSCLC group were significantly lower compared with those in the healthy control group but not significantly different from those in the benign lung lesions group (58). Thus far, the specific value of the role of miR-126 in early NSCLC and benign lung lesions still needs to be clarified further. Zhu *et al* (59) reported that circulating miRNAs, including miR-126, had a good diagnostic value for lung cancers, with a sensitivity of 60.7%, a specificity of 92.5%, and an AUC of 79.3%. It is also worth noting that further logistic regression model analysis revealed that the combination of miR-126, miR-182, miR-183 and miR-210 with carcinoembryonic antigen substantially increased the diagnostic value, with an AUC of 96.5%; sensitivity, 81.2%; specificity, 100.0%; and accuracy, 90.8% (59). The aforementioned results indicated that circulating miR-126, particularly in combination with multiple other miRNAs, may serve as a promising biomarker for the diagnosis of lung cancer (56,59,60).

In addition, Bagheri *et al* (61) reported that a composite analysis of miR-145, miR-126 and miR-7 in sputum produced

90% sensitivity and 90% specificity in distinguishing patients with NSCLC from controls. In addition, the combination of these three aforementioned miRNAs demonstrated an AUC value of 93%, which was notably higher compared with the 53-88% AUC values of the individual miRNAs (61). Of note, more studies demonstrated that bronchoalveolar lavage fluid exosomal miR-126 was highly expressed in lung adenocarcinoma tissues compared with normal tissue samples, suggesting that exosomal miR-126 may be a potential biomarker for NSCLC diagnosis (14,62). These data reflect the promising value of different sources of miR-126 in the diagnosis of NSCLC patients.

#### 4. miR-126 and lung cancer prognosis

In the past decade, a large number of studies have documented that miR-126 may also be a meaningful prognostic marker of lung cancer (19,21,63-65) (Table II). Recently, Xu *et al* (66) found that high plasma expression level of miR-126 in patients with lung cancer was associated with shorter disease-free survival [hazard ratios (HRs) of univariate Cox and multivariate Cox were 1.867 and 1.582, respectively; 95% confidence intervals (CIs) of univariate Cox and multivariate Cox were 1.386-2.515 and 1.158-2.161, respectively] and overall survival (OS) (HRs of univariate Cox and multivariate Cox were 1.706 and 1.320, respectively; 95% CIs of univariate Cox and multivariate Cox were 1.218-2.388 and 0.932-1.817, respectively).

Table I. Targets of miR-126 in lung cancer tumorigenesis.

Experimental setting	Regulation of miR-126	Targets	Effects	(Refs.)
<i>In vitro</i> , A549 cells	Overexpression knockdown	STAT3	Proliferation, migration, cell cycle entry, apoptosis susceptibility	(16)
<i>In vitro</i> , H1299 cells	Inhibitor, constructed by Vipotion Co., Ltd.	VEGF-A/ VEGFR-2/ERK	Proapoptosis, antimetastasis	(17)
<i>In vitro</i> , H69AR cells	Overexpression	PI3K/AKT/mTOR	Growth of NSCLC cells	(18)
<i>In vitro</i> , H69AR cells	Overexpression	VCAM-1	Growth of NSCLC cells	(18)
<i>In vitro</i> , A549 cells	Overexpression	Hub genes (VEGFA, AKT1 and KRAS)	Invasion of NSCLC cells	(19)
<i>In vitro</i> , A549, H1975, H1299 and HCC827 cells <i>In vivo</i> , mice	Overexpression	CCR1	Growth, migration and invasion of NSCLC cells Reduced tumor growth	(20)
<i>In vitro</i> , A549, H1975, H1299, H460 and SPC-A1 cells	Inhibitor, constructed by Shanghai Genepharma Co. Ltd.	SLC7A5	Angiogenesis, growth, migration and invasion of NSCLC cells	(21)
<i>In vitro</i> , SPC-A1, LLC cells <i>In vivo</i> , mice	Overexpression	PI3K/AKT/Snail	EMT The weight of the Lewis lung carcinoma-derived primary tumors increased	(27)
<i>In vitro</i> , A549 cells	Overexpression inhibitor, not mentioned	PTEN/PI3K/AKT	Migration and invasion of NSCLC cells	(10)
<i>In vitro</i> , 4T1-M cells <i>In vivo</i> , mice	Overexpression	SDF-1 $\alpha$	Recruitment of mesenchymal stem cells Reduced tumor growth	(29)
<i>In vitro</i> , A549 cells <i>In vivo</i> , mice	Overexpression	EGFL7, IRS-1	Angiogenesis Inhibited tumor initiation	(40)
<i>In vitro</i> , A549, H1703, H226, H358, HMVEC, NHBE and DMS53 cells <i>In vivo</i> , mice	Overexpression	Crk	Angiogenesis, growth, migration and invasion of NSCLC cells Inhibited tumor initiation	(40,22)
<i>In vitro</i> , endothelial cells <i>In vivo</i> , zebrafish	Knockdown	Spred1/MAPK/VEGF p3kr2/PI3K/VEGF	Angiogenesis Loss of vascular integrity and hemorrhage during embryonic development	(50)

EGFL7, epidermal growth factor-like domain-containing gene 7; SLC7A5, solute carrier family 7 (cationic amino acid transporter, y+ system), member 5; NSCLC, non-small cell lung cancer; IRS-1, insulin receptor substrate 1; Crk, v-crk sarcoma virus CT10 oncogene homologue; Spred1, sprouty-related EVH1 domain-containing protein 1; MAPK, MAP kinase; VEGF, vascular endothelial growth factor; p3kr2, gene p3kr2; PI3K, phosphatidylinositol-3 protein kinase; STAT3, signal transducer and activator of transcription 3; VEGF-A, vascular endothelial growth factor A; ERK, extracellular protein kinase; AKT, protein kinase B; mTOR, mechanistic target of rapamycin; VCAM-1, vascular cell adhesion molecule 1; VEGFA, vascular endothelial growth factor A; AKT1, protein kinase B1; KRAS, Kirsten rat sarcoma viral oncogene homologue; CCR1, chemokine (C-C motif) receptor 1; EMT, epithelial-mesenchymal transition; PTEN, phosphatase and tensin homolog; SDF-1 $\alpha$ , stromal cell-derived factor-1 $\alpha$ ; GRM8, glutamate receptor metabotropic 8; DACH1, dachshund family transcription factor 1; miR, microRNA.

In addition, not only was the expression of miR-126 apparently downregulated in tumor tissue compared with benign control tissue in NSCLCs, but the expression level was also significantly higher in NSCLCs with a tumor size of  $\leq 3$  cm compared with those with a tumor size of  $>3$  cm, indicating the association between miR-126 expression and tumor size (67). In addition, Jusufovic *et al* (68) reported that low expression of miR-126 in lung cancer tissue was a negative prognostic factor for progression-free survival (PFS) (HR, 0.10; 95% CI, 0.04-0.21) and OS (HR, 0.14; 95% CI, 0.06-0.31) in patients

with NSCLC, which may be related to elevated MVD and lung cancer angiogenesis. Finally, Lønvik *et al* (69) discovered that intranuclear miRNA processing enzyme Drosha/miR-126 coexpression had a negative impact on the disease-specific survival rate. Additionally, lower expression of combined miRNAs (let-7b and miR-126) was closely associated with lower PFS time (HR, 0.05; 95% CI, 0.02-0.14) and OS time (HR, 0.05; 95% CI, 0.02-0.16) in patients with NSCLC (68). However, the possible difference in the prognostic value between single miR-126 and coexpression of miR-126 with

Table II. Biomarker value of miR-126 in the diagnosis and prognosis of lung cancer.

A, Diagnosis						
Methods using miR-126 as a diagnostic biomarker	Source	Specificity (%)	Sensitivity (%)	AUC (%)	Clinical stage	(Refs.)
Single	Serum	84.00	96.40	87.40	I-IV stage of lung cancer NSCLC metastasis	(55)
Single	Serum plasma	78.00	79.00	90.00	I-II stage of lung cancer	(56)
miR-222/miR-126	Serum	70.00	80.00	66.00	Asbestos-related NSCLC	(57)
Single	Serum exosomes	-	-	-	I-II stage of lung cancer	(58)
Multiple miRNAs/ miR-126	Serum plasma	87.00	87.00	94.00	I-II stage of lung cancer	(56)
CEA/miR-126	Serum exosomes	100.00	81.20	96.50	0-IIIB stage of lung cancer	(59)
CEA/miR-126	Serum exosomes	92.50	88.50	97.50	0-I stage of lung cancer	(59)
Single, multiple miRNAs/miR-126	Sputum	90.00	90.00	93.10	I-IV stage of lung cancer	(61)
Exosomal	Tissue	-	-	-	I-II stage of lung cancer	(14)
B, Prognosis						
Methods using miR-126 as a prognostic biomarker	Source	DFS HRs (95% CIs)	PFS HRs (95% CIs)	OS HRs (95% CIs)	Clinical stage	(Refs.)
Single	Plasma	1.867 (1.39-2.51)	-	1.706 (1.22-2.39)	I-III stage of lung cancer	(66)
Single	Tissue	-	-	2.27 (0.83-6.23)	I-IV stage of lung cancer	(67)
Single	Tissue	-	0.10 (0.04-0.21)	0.14 (0.06-0.31)	II-IV stage of lung cancer	(68)
Drosha/miR-126	Tissue	-	-	-	I-III stage of lung cancer	(69)
let-7b/miR-126	Tissue	-	0.05 (0.02-0.14)	0.05 (0.02-0.16)	II-IV stage of lung cancer	(68)

AUC, area under the curve; NSCLC, non-small cell lung cancer; CEA, carcinoembryonic antigen; DFS, disease-free survival; HRs, Hazard ratios; CIs, confidence intervals; PFS, progression-free survival; OS, overall survival; Drosha, intranuclear miRNA processing enzyme Drosha; miRNA, microRNA.

other factors in patients with NSCLC prognosis needs to be further elucidated. In brief, the aforementioned results may contribute to proving the prognostic value of miR-126 in lung cancer.

### 5. miR-126 as a potential target for lung cancer therapy

Currently, some drugs for treating lung cancer target the VEGF signaling pathway (70-72). VEGF signaling can promote the growth of vascular endothelial cells and vascular repair through connexin 43 (17,73-78). miR-126 was reported as one of the most important regulators of signaling for angiogenic growth factors, such as VEGF, fibroblast growth factor, insulin like growth factor and endothelial growth factor that manipulate

vascular integrity and angiogenesis, indicating its potential value in lung cancer treatment (40,53) (Table III). For instance, Sun *et al* (40) first reported that the expression of EGFL7 increased significantly *in vitro* and *in vivo* after transfection with a miR-126 overexpression plasmid that targets EGFL7. Subsequently, miR-126 restoration led to a reduction in the number of A549 cell initiating differentiation, accompanied by significant inhibition of tumor cell proliferation *in vitro* and tumor formation *in vivo* (40). Recently, Jia *et al* (27) used a xenograft Lewis lung carcinoma model in C57BL/6 mice to detect the role of miR-126 in lung cancer metastasis and found that the stable ectopic expression of miR-126 significantly suppressed the formation of lung metastases following the surgical removal of the primary tumors. Meanwhile, decreased

Table III. miR-126 as a potential target for lung cancer therapy.

A, Methods targeting miRNA-126				
Expression of miR-126	Experimental setting	Targets	Effects	(Refs.)
Upregulated	<i>In vitro, in vivo</i>	EGFL7	Inhibition on initiating cell differentiation, tumour cells proliferation and tumor formation	(40)
Upregulated	<i>In vitro, in vivo</i>	PI3K/AKT/Snail	Inhibition on lung cancer metastasis, EMT	(27)
Upregulated	<i>In vitro</i>	VEGF/PI3K/AKT/MRP1	Promoting the sensitivity of NSCLC cells to anticancer agents	(3)
Upregulated	<i>In vivo</i>	PI3K-AKT	Promoting ionizing radiation-induced apoptosis	(79,80)
B, Methods using miR-126 differently				
Expression of miR-126	Experimental setting	Targets	Effects	(Refs.)
lncRNA-PVT1-5/ miR-126	<i>In vitro</i>	SLC7A5	Inhibition on tumorigenesis	(81)
miR-126-231-Exo	<i>In vitro, in vivo</i>	PTEN/PI3K/AKT	Inhibition on tumorigenesis	(82)
C, Other drugs/methods				
Expression of miR-126	Experimental setting	Targets	Effects	(Refs.)
Cryptotanshinone	<i>In vitro</i>	STAT3	Inhibition of the growth of lung cancer cells	(16)
TBMS1	<i>In vitro</i>	VEGF-A/VEGFR-2/ERK	Pro-apoptosis, anti-metastasis	(17)
CT-PRFA	<i>In vivo</i>	-	Inhibition of tumorigenesis	(88)

EGFL7, epidermal growth factor-like domain-containing gene 7; PI3K, phosphatidylinositol-3; AKT, protein kinase B; EMT, epithelial-mesenchymal transition; NSCLC, non-small cell lung cancer; VEGF, vascular endothelial growth factor; MRP1, resistance-associated protein 1; lncRNA-PVT1-5, long non-coding RNA-PVT1-5; SLC7A5, solute carrier family 7 (cationic amino acid transporter, y+ system), member 5; miR-126-231-Exo, miR-126 loaded into 231-Exo; PTEN, phosphatase and tensin homologue; STAT3, signal transducer and activator of transcription 3; TBMS1, tubeimoside-1; VEGF-A, vascular endothelial growth factor A; VEGFR-2, vascular endothelial growth factor receptor 2; ERK, extracellular protein kinase; CT-PRFA, computed tomography-guided percutaneous radio frequency ablation, miRNA, microRNA.

expression of EMT markers was observed in the miR-126 overexpression group compared with the negative control group. The results of the aforementioned study indicated that miR-126 could suppress EMT and metastasis of lung cancer cells by targeting PI3K/AKT/Snail signaling (27). Enhanced expression of miR-126 also increased the sensitivity of NSCLC cells to anticancer agents through the negative regulation of the VEGF/PI3K/AKT/resistance-associated protein 1 signaling pathway (3). Notably, some studies also demonstrated that miR-126 could promote ionizing radiation-induced apoptosis through the PI3K-AKT pathway in lung cancer (79,80).

In addition to the studies mentioned above, miR-126 was also regarded as a crucial regulator involved in the effect of other factors in lung cancer (Table III). For instance, Li *et al* (81) reported that long non-coding RNA-PVT1-5 (lncRNA-PVT1-5) may act as a competing endogenous RNA for miR-126 to promote cell proliferation by regulating the miR-126/SLC7A5 pathway, suggesting that the lncRNA-PVT1-5/miR-126/SLC7A5 regulatory network may

shed light on tumorigenesis in lung cancer. Furthermore, exosomes are a delivery systems with low immunogenicity and toxicity that are not recognized by the mononuclear phagocyte system (82). These special properties of exosomes make them appropriate to serve as targeted delivery systems in cancer therapy (83,84). Recently, Nie *et al* (85) demonstrated that miR-126 loaded into 231-Exo (miRNA-231-Exo) led to an effective inhibitory effect on proliferation and migration in A549 lung cancer cells via the interruption of the PTEN/PI3K/AKT signaling pathway. miR-126-laden 231-Exo, which can effectively escape innate immune cells, also demonstrated a potent cancer inhibition effect in a lung cancer metastasis model in mice.

In addition, miR-126 also serves a vital role when other therapeutic approaches using other drugs are used in lung cancer. For instance, cryptotanshinone is an important inhibitor of the development of lung cancer cells (86). The expression levels of miR-126 were upregulated by treatment with cryptotanshinone in A549 cells (87). In addition, one

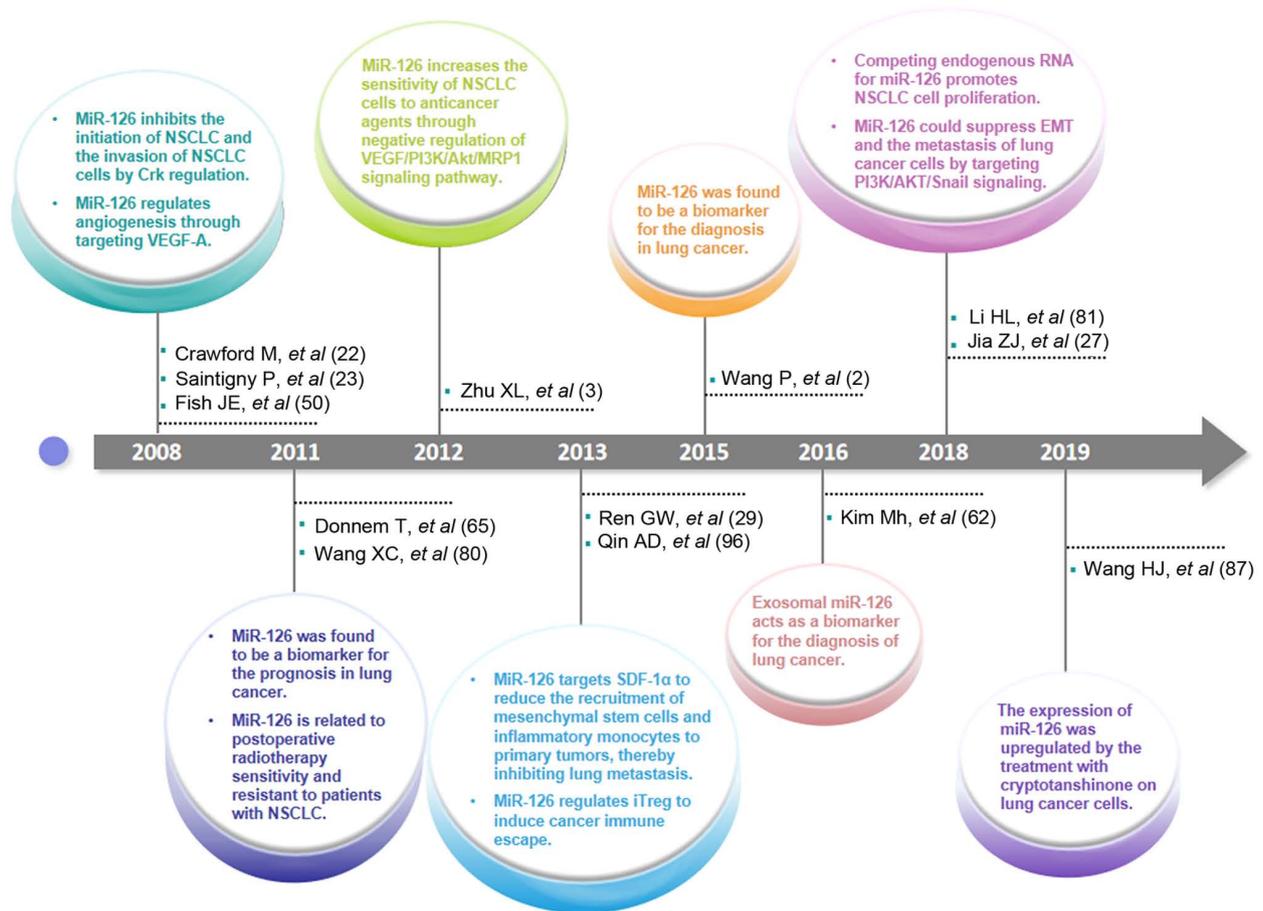


Figure 2. Highlights in the research progress of miR-126 in lung cancer. In 2008, it was first mentioned that miR-126 has a significant role in the angiogenesis, initiation and progression of lung cancer, as well as lung cancer cell invasion. MiR-126 was viewed as a prognostic biomarker in lung cancer and first reported that it is related to postoperative radiotherapy sensitivity and resistant to patients with NSCLC in 2011. Afterwards, the role of miR-126 in the sensitivity of NSCLC cells to anticancer agents was uncovered in 2012. In 2013, a seminal publication reported the role of miR-126 in the recruitment of mesenchymal stem cells and inflammatory monocytes in lung metastasis. Due to the discovery of the role of miR-126 in the lung tumor microenvironment, its role in cancer immune escape which is mediated by iTregs was found. Thereafter, miR-126 and exosomal miR-126 were perceived as diagnostic biomarkers for lung cancer since 2015 and 2016, respectively. In 2018, reports about competing endogenous RNA for miR-126 promoting NSCLC cell proliferation and the role of miR-126 in EMT and the metastasis of lung cancer cells were published. In 2019, changes in the expression level of miR-126 in lung cancer cells following treatment with cryptotanshinone were reported. miR, microRNA; NSCLC, non-small cell lung cancer; EMT, epithelial-mesenchymal transition; Crk, v-crk sarcoma virus CT10 oncogene homologue; VEGF, vascular endothelial growth factor; VEGF-A, vascular endothelial growth factor A; MRP1, resistance-associated protein 1; SDF-1 $\alpha$ , stromal cell-derived factor-1 $\alpha$ ; iTreg, induced T regulatory cell; AKT, protein kinase B; PI3K, phosphatidylinositol-3 protein kinase.

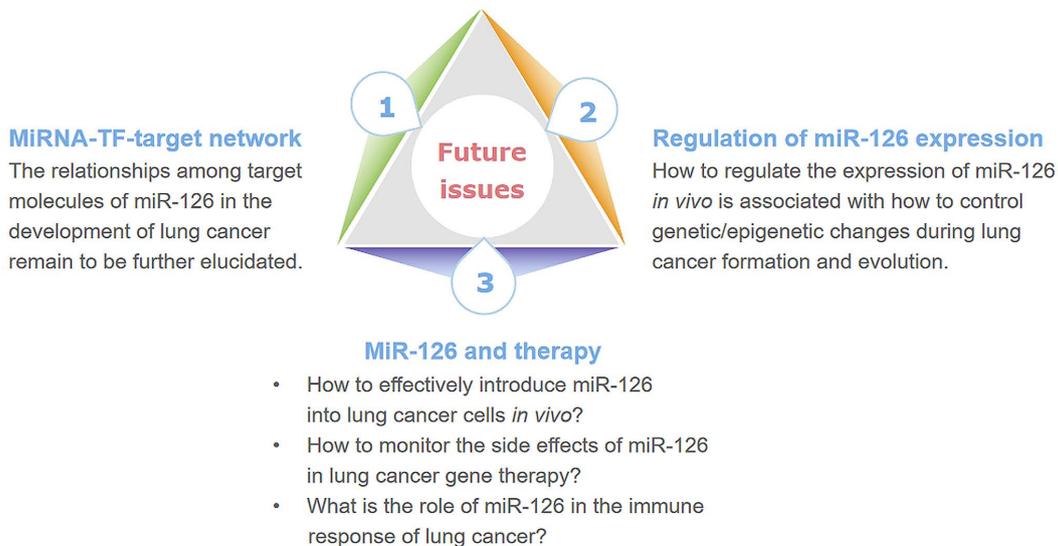


Figure 3. A schematic of future issues associated with miR-126 in lung cancer. The major issues may be from three important fields: The target network, regulation of miR-126 expression and therapy in lung cancer. miR, microRNA; TF, transcription factors.

new study demonstrated that tubeimoside-1 (TBMS1) could elevate miR-126 expression, whereas overexpressing miR-126 inactivated the VEGF-A/VEGFR-2/ERK signaling pathway, which promoted proapoptotic and antimetastatic effects in NCI-H1299 cells (17). The aforementioned study may offer a theoretical foundation for miR-126 serving a critical role in the treatment of TBMS1 in lung cancer (17). Similarly, other researchers reported that computed tomography-guided percutaneous radio frequency ablation was an effective treatment for primary NSCLCs and secondary lung tumors in hepatocellular carcinoma; the efficacy of ablation may be related to its ability to normalize deregulated expression of miR-126 (88).

## 6. Conclusion

To date, important progress in the research on the role of miR-126 in the tumorigenesis, diagnosis, prognosis and therapy of lung cancer has been achieved (Fig. 2). However, some scientific issues remain to be further elucidated (Fig. 3). Firstly, the relationships among different target molecules of miR-126 in the development of lung cancer have not yet been clearly elucidated. Notably, Barshack *et al* (89) demonstrated that miR-126 was significantly upregulated in liver cancer lung metastasis, indicating that miR-126 may play different roles through distinct targets in some special types of cancer (90,91). For instance, in lung tumor tissues, Tafsiri *et al* (90) reported that miR-126 was downregulated in 15 out of 18 adenocarcinoma samples, but there was no significant correlation between squamous cell carcinoma and expression of miR-126. Chen *et al* (91) demonstrated the result of pathway enrichment analysis of the target genes that the target genes of miR-126 in NSCLC [FOXO3, phosphoinositide 3-kinase catalytic subunit  $\delta$  (PIK3CD) and PIK3R2] were different from those in colorectal cancer (Bcl-2, PIK3CD, PIK3R2). The underlying molecular mechanisms may be related to the involvement of miR-126 in an miRNA-TF-target network that contains PIK3CD, PIK3R2, forkhead box protein O3, plexin B2 and tuberous sclerosis 1 (91). Secondly, some challenges need to be further addressed. For example, it is unclear how to effectively introduce miR-126 into lung cancer cells *in vivo* and how to monitor the side effects of miR-126 in lung cancer gene therapy. In particular, some evidences have shown that miR-126 also plays a vital role in the function of immune cells including effector T cells and regulatory T cells (Tregs) (92-96). Additionally, miR-126 is also likely to be involved in CD4<sup>+</sup> T cell function (97). Hence, further investigation of the role of miR-126 in lung cancer, including in the immune response, may be valuable for the progression of miRNA-based immunotherapy against lung cancer.

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## Availability of data and materials

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

## Authors' contributions

QC designed and wrote the study. SC and YZ designed the the study. JZ wrote the manuscript. LX conceived, designed and wrote the manuscript. All authors have read and approved this manuscript.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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