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MicroRNA-mediated regulation in lung adenocarcinoma: Signaling pathways and potential therapeutic implications (Review)

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Abstract. Lung adenocarcinoma (LUAD) poses a significant global health burden owing to its high incidence rate and unfavorable prognosis, driven by frequent recurrence and drug resistance. Understanding the biological mechanisms underlying LUAD is imperative to developing advanced therapeutic strategies. Recent research has highlighted the role of dysregulated microRNAs (miRNAs) in LUAD progression through diverse signaling pathways, including the Wnt and AKT pathways. Of particular interest is the novel pathological mechanism involving the interaction between competing endogenous RNAs (ceRNAs) and miRNAs. This review critically analyzed the impact of aberrant miRNA expression on LUAD development, shedding light on the associated signaling pathways. It also highlighted the emerging significance of ceRNA-miRNA interactions in LUAD pathogenesis. Elucidating the intricate regulatory networks involving miRNAs and ceRNAs presents a promising avenue for the development of potential therapeutic interventions and diagnostic biomarkers in LUAD. Further research in this area is essential to advance precision medicine approaches and improve patient outcomes.

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Key words: biological mechanisms, competing endogenous RNA interactions, drug resistance, incidence rate, prognosis, recurrence

Contents

1. Introduction

Lung cancer has one of the highest cancer incidence rates globally (1). It is the leading cause of cancer-related deaths, with a five-year survival rate of only 15% (2). Among the numerous pathological tissue types, adenocarcinoma is the most prevalent (3). The prognosis of lung adenocarcinoma (LUAD) is often poor due to tumor heterogeneity, delayed diagnosis and drug resistance (4). Despite the emergence of new therapies, including immunotherapy and targeted therapy, LUAD remains a global public health concern (5). Moreover, fluctuations in oncogene expression patterns and a limited understanding of LUAD pathogenesis have caused bottlenecks in the development of effective treatments for LUAD (6). Therefore, genomic medicine has increasingly gained prominence as an essential topic to address the gaps in tumor pathogenesis research.

~2% of the human genome encodes proteins (7). The remaining 98% of the non-coding portion has received considerable scientific attention over the past few decades (8). Previous studies have demonstrated that non-coding RNA (ncRNA) is involved in various cellular and physiological processes (9). They have been found to play a role in human health and pathological conditions such as LUAD (10). MicroRNAs (miRNAs) are endogenous ncRNAs that play crucial roles in the post-transcriptional regulation of genes. Accumulating evidence confirms that miRNAs are involved in the regulation of LUAD via specific pathways. The expression of these miRNAs indicates the emergence of an active

signaling marker (11). The present review analyzed the role of miRNAs in LUAD development and highlighted the potential pathways involved.

General characteristics of miRNAs and mode of action. miRNAs are a class of non-coding single-stranded RNA molecules with lengths of ~22-24 nucleotides. They are widely present in animals, plants and viruses (12). Pri-miRNA is produced by RNA polymerase II via a clear miRNA-processing mechanism (13). Subsequently, pri-miRNA is transformed into pre-miRNA through the processing of RNase III, Drosha and DGCR8 (14). DGCR8 identifies double-stranded structures and recruits substrates (15). Drosha is responsible for cleaving pri-miRNAs. This process occurrs as the first shear in the nucleus. The newly generated pre-miRNA is transferred to the cytoplasm through RANGTP/exportin-5 (16).

The ribonuclease Dicer then combines with the TRBP protein to synthesize a mature double-stranded miRNA from pre-miRNA (17). In the process of assembling miRNA particles, the RNA helicase separates the two strands of duplex miRNA (18). The 5' end of the single strand forms an active double strand with its partner, which enters a complex containing miRNA and ribonucleoprotein particles (19). The other strand breaks down (20). After a series of reactions, single-stranded miRNAs combine with Argonaute (2) in RNA-induced silencing complexes and then bind to the 3' untranslated region of the target mRNA, leading to translation suppression or de-adenylation (Fig. 1) (21). In recent years, numerous studies have confirmed that miRNAs are associated with numerous diseases, such as diabetic kidney disease (22) and neurodegenerative disorders (23). In addition, miRNAs are known to participate in various malignant biological behaviors of tumors, such as proliferation and epithelial-mesenchymal transition (EMT) (24,25) (Table I).

Determination of miRNAs in LUAD. RNA microarrays and sequencing have been widely used to screen differentially expressed miRNAs in LUAD. The results were validated using reverse transcription-quantitative polymerase chain reaction (RT-qPCR) (102). Bioinformatics was employed to identify downstream target genes and enriched pathways (103). Petkova *et al* (104) used 12 pairs of tissues to screen 107 significantly dysregulated miRNAs through microarrays and performed RT-qPCR validation on the obtained results using 50 pairs of samples. A total of eight significantly differentially expressed miRNAs were successfully validated. Gene Ontology and Kyoto Encyclopedia of Genes and Genomes analyses revealed enrichment in the cell cycle, gene expression and EGFR pathways. The present study highlighted the potential of exploring differential miRNA expression profiles to understand their impact on tumor diagnosis and prognosis (104). Beyond human 365, it can also be detected in plasma. Jin *et al* (105) performed next-generation sequencing on samples from 16 patients with LUAD and 12 healthy individuals. Subsequently, a validation set including 10 LUAD patients and 30 healthy individuals was used to confirm significant differential expression of four miRNAs, including miR-181-5p. These miRNAs were further evaluated for diagnostic accuracy in an additional 60 patients initially diagnosed with non-small cell lung cancer, resulting in an area under curve (AUC) value of 0.936. These results revealed that these miRNAs may be promising biomarkers for diagnosing LUAD (105).

2. Role of miRNA in LUAD

Various studies have shown that miRNAs play an important role in regulating tumor biological behavior and influencing the tumor microenvironment (106,107). Numerous miRNAs have been recognized as tumor markers and therapeutic targets that play prominent roles in tumor prevention, diagnosis and treatment (108). Next, the roles of miRNAs in LUAD were investigated.

miRNAs as biomarkers in LUAD. Over the past 20 years, studies have confirmed that miRNAs can serve as biomarkers of malignant tumors, including LUAD (109,110). Tong *et al* (111) found that *miRNA-365* is significantly downregulated in LUAD, and its expression is associated with tumor invasion and migration as well as patient survival. Meanwhile, miR-365 upregulates *ETS1* expression and inhibits EMT by inactivating the AKT/mTOR pathway (111). Kim *et al* (112) also reported that high *miRNA-130b* expression is significantly associated with unfavorable clinicopathological parameters and poor survival outcomes in LUAD. Another study revealed a significant decrease in *miR-339-5p* expression in LUAD tissues and plasma, whereas *miR-21* expression was significantly elevated. Receiver operating curve analysis demonstrated that they could be distinguished from normal control individuals through the AUC. This result confirmed the role of miRNAs in the early screening of LUAD (113). These miRNAs may serve as targeted tools for the diagnosis and evaluation of LUAD prognosis. Several studies have demonstrated that miRNAs are involved in the biological processes of LUAD in addition to acting as biomarkers. Subsequently, a series of specific miRNA functions were presented to demonstrate their significant roles in LUAD.

Role of miRNAs in the malignant biological behavior of LUAD: Cell proliferation and apoptosis. Cell proliferation and apoptosis are common in tumors. Together, they constitute the 'minimum platform' for the further development of tumors (114). To date, research on miRNAs in the field of tumor cell proliferation and apoptosis has been the most extensive. *MiR-144-5p* is considered a tumor suppressor gene in ovarian and lung cancers. It is involved in almost all stages of tumor development (115,116). Luo *et al* (28) found a negative regulatory relationship between *miR-144-5p* and *CDCA3*; *miR-144-5p* inhibited cell proliferation and promoted apoptosis through the interaction between CDCA3 and p53 signaling pathways. This result indicated that the downregulation of *miR-144-5p* had an antitumor effect by affecting the activation of p53.

Another study confirmed that *miR-195-5p* is expressed at low levels in LUAD and can negatively upregulate its target gene, TrxR2. *MiR-195-5p* inhibits cell proliferation by arresting the cell cycle phase (39). A previous study revealed that *miR-3941* was significantly downregulated in LUAD tissues and cells, and miR-3941 bound to IGBP1, thereby inhibiting its transcription. Overexpression of *miR-3941* not

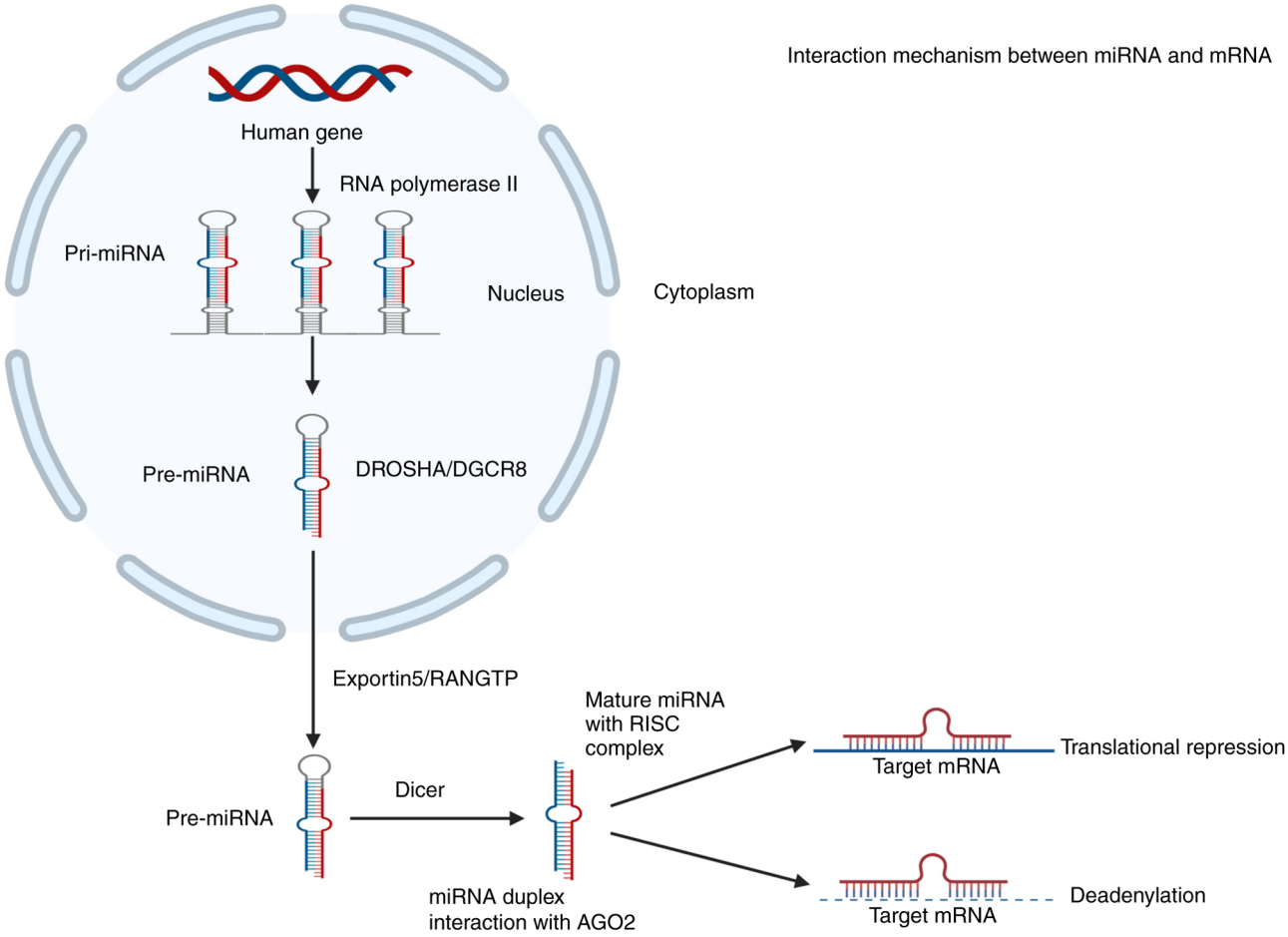

Figure 1. The production process of miRNA and its role in mRNA expression.

only inhibited the cell cycle but also induced the production of caspase-3 (44). Previous studies also demonstrated that other miRNAs, such as *miR-383-5p, miR-335-3p*, and *miR-216b-3p*, were all downregulated in LUAD, inhibited cell proliferation, and promoted apoptosis (43,45,54).

Correspondingly, various tumor promoters, such as miR-516a-3p, have been reported to promote cancer cell proliferation and inhibit apoptosis by regulating *PTPRD* expression. Researchers also found a significant relationship between the expression of miR-516a-3p and the clinical staging of LUAD (61). Thus, these molecules are potential targets for the diagnosis and treatment of LUAD.

Correlation of miRNA with LUAD invasion and metastasis. As a malignant tumor, LUAD can grow rapidly *in situ* and spread to distal organs via blood circulation and lymphatic tissue (117). Invasion and metastasis are important factors in the sustained progression of LUAD, and their mutual influence leads to lower survival rates (118). Strong evidence suggests that miRNAs participate in tumor invasion and metastasis by regulating the expression of their target genes. Mo *et al* (29) validated the differential expression of *miR-145* in LUAD tissues and found that the upregulation of miR-145 inhibited the invasion and metastasis of SPC-A1 and A549 cell lines. They also confirmed that *miR-145* mediated this process by influencing the translation of N-cadherin, a known cell adhesion molecule. At the clinical level, the findings revealed a strong correlation between low *miR-145* expression and a high metastasis rate (29). Furthermore, a previous study demonstrated that *miR-937-3p* promotes the angiogenesis, invasion and metastasis of LUAD cells. MiR-937-3p has been reported to simultaneously regulate E-cadherin, vimentin, Slug and N-catenin, all of which are considered classic biomarkers of angiogenesis. Moreover, additional evidence was provided that the upstream oncogenic factor (MYC) of *miR-937-3p* binds to and upregulates its promoter region (37). Wu *et al* (48) demonstrated that *miR-196b* is upregulated in LUAD and is significantly correlated with an adverse prognosis. The knockdown of *miR-196b* delayed the invasion and metastasis of LUAD cells (48).

EMT is a cellular process in which cells lose their epithelial and interstitial properties. During tumor evolution, EMT is closely related to tumor occurrence, metastasis and treatment resistance (119). Long *et al* (26) showed that *miR-214* is overexpressed in LUAD and promotes metastasis and EMT by regulating *Sufu*. During this process, epithelial and interstitial marker genes showed significant changes in opposite directions. Simultaneously, knockdown of *miR-214* was shown to suppress EMT activity (26).

Other miRNAs, such as *miR-485*, *miR-138-5p* and *miR-1827*, regulate EMT in LUAD cells and affect LUAD progression. These miRNAs are associated with tumor

Table I. Dysregulated miRNAs in lung adenocarcinoma.

miRNA	Expression	Target	Role in LUAD	(Refs.)
miR-214	Upregulated	Sufu	EMT, metastasis	(26)
miR-106a	Upregulated	TP53INP1	Autophagy, EMT, metastasis	(27)
miR-144-5p	Downregulated	CDCA3	Cell proliferation, apoptosis	(28)
miR-145	Downregulated	N-cadherin	Invasion, migration	(29)
	Downregulated	OCT4	Cell proliferation	(30)
miR-32-5p	Downregulated	SMAD3	Invasion, migration	(31)
miR-148a	Downregulated	E2F3	Cell proliferation	(32)
miR-9-5p	Upregulated	STARD13	Cell proliferation, migration	(33)
	Upregulated	ID4	Cell proliferation, invasion, migration	(34)
miR-29a	Downregulated	CEACAM6	Cell proliferation, migration, invasion	(35)
miR-192	Upregulated	Bcl-2	Chemo-resistance	(36)
miR-937-3p	Upregulated	SOX11	Angiogenesis, invasion, metastasis	(37)
miR-195-5p	Downregulated	PTBP1	Cell proliferation, migration	(38)
	Downregulated	TrxR2	Cell proliferation, invasion, migration, apoptosis	(39)
	Downregulated	HOXA10	Radiosensitivity	(40)
miR-202-3p	Downregulated	RRM2	Cell proliferation, metastasis	(41)
miR-30e-5p	Upregulated	PTPN13	Cell proliferation	(42)
miR-383-5p	Downregulated	CIP2A	Cell proliferation, apoptosis	(43)
miR-3941	Downregulated	IGBP1	Cell proliferation, apoptosis	(44)
miR-335-3p	Downregulated	COPB2	Cell proliferation, apoptosis, migration	(45)
miR-204	Downregulated	SOX4	Metastasis	(46)
miR-195	Downregulated	Apelin	Cell proliferation, invasion	(47)
miR-196b	Upregulated	AQP4	Invasion, migration	(48)
miR-3666	Downregulated	BPTF	Cell proliferation, invasion, migration	(49)
miR-485	Downregulated	Flot2	EMT, metastasis	(50)
miR-134	Downregulated	FOXM1	Multidrug resistance	(51)
miR-873	Upregulated	SRCIN1	Cell proliferation, migration	(52)
miR-29c	Downregulated	VEGFA	Cell proliferation, invasion, migration, angiogenesis	(53)
miR-216b-3p	Downregulated	PBK, TOPK	Cell proliferation, apoptosis	(54)
miR-138-5p	Downregulated	ZEB2	Cell proliferation, metastasis, EMT	(55)
miR-590	Upregulated	OLFM4	Invasion, migration	(56)
miR-182	Upregulated	PDCD4	Cell proliferation, invasion, migration	(57)
miR-576-3p	Downregulated	SGK1	Invasion, migration	(58)
miR-520c-3p	Downregulated	AKT1, AKT2	Cell proliferation, invasion, migration	(59)
miR-1827	Downregulated	MYC, FAM83F	Cell proliferation, metastasis, EMT, invasion, apoptosis	(60)
miR-516a-3p	Upregulated	PTPRD	Cell proliferation, apoptosis, migration, invasion	(61)
miR-30a-5p	Downregulated	VCAN	Cell proliferation, metastasis, EMT, invasion	(62)
	Downregulated	CCNE2	Cell proliferation, invasion, migration	(63)
miR-130-5p	Downregulated	EZH2	Invasion, migration	(64)
miR-1205	Downregulated	APC2	Cell proliferation	(65)
miR-144-3p	Downregulated	IRS1	Invasion, metastasis	(66)
miR-200b-3p	Upregulated	ABCA1	Cell proliferation, metastasis	(67)
miR-550a-5p	Upregulated	LIMD1	Cell proliferation	(68)
miR-297	Upregulated	GPC5	Cell proliferation, invasion, migration	(69)
miR-197-3p	Upregulated	CYLD	Cell proliferation, apoptosis	(70)
miR-505-5p	Upregulated	TP53AIP1	Cell proliferation, apoptosis	(71)

Table I. Continued.

miRNA	Expression	Target	Role in LUAD	(Refs.)
miR-938	Upregulated	RBM5	Cell proliferation	(72)
miR-885-3p	Downregulated	Aurora A	Chemo-resistance	(73)
miR-139-5p	Downregulated	CCNB1	Cell proliferation, invasion, migration	(74)
	Downregulated	MAD2L1	Cell proliferation, invasion, migration	(75)
miR-660	Downregulated	SATB2	Cisplatin resistance	(76)
miR-147b	Upregulated	MFAP4	Cell proliferation, invasion, migration	(77)
miR-140-3p	Downregulated	TYMS	Cell proliferation, invasion, migration, angiogenesis	(78)
miR-30a-3p	Downregulated	CNPY2	Cell proliferation, migration	(79)
miR-30b-3p	Downregulated	COX6B1	Cell proliferation, invasion	(80)
miR-3648	Upregulated	SOCS2	Cell proliferation, invasion, migration	(81)
miR-96-5p	Upregulated	ARHGAP6	Cell proliferation, invasion, migration	(82)
	Upregulated	FHL1	Cell proliferation, invasion, migration	(83)
miR-218-5p	Downregulated	ERO1A	Cell proliferation, invasion, migration	(84)
miR-1-3p	Downregulated	CELSR3	Cell proliferation, invasion, migration	(85)
	Downregulated	PRC1	Cell proliferation, invasion	(86)
miR-944	Downregulated	STAT1	Cell proliferation	(87)
miR-186-5p	Upregulated	PTEN	Cell proliferation, invasion, migration	(88)
miR-196b-5p	Upregulated	RSPO2	Cell proliferation, invasion, migration	(89)
miR-22-3p	Downregulated	TP53	Cell proliferation, invasion, migration, apoptosis	(90)
miR-451	Downregulated	MIF	Cell proliferation, migration	(91)
miR-21-5p	Upregulated	WWC2	Cell proliferation, invasion, migration	(92)
miR-486-5p	Downregulated	SAPCD2	Cell proliferation, invasion, migration, apoptosis	(93)
miR-93-5p	Upregulated	PTEN, RB1	Cell proliferation, invasion, migration, apoptosis	(94)
miR-326	Downregulated	PD-L1, B7-H3	Immune escape, metastasis	(95)
miR-3677-3p	Upregulated	KLF12	Cell proliferation, invasion, migration	(96)
miR-145	Downregulated	OCT4	EMT, metastasis	(97)
miR-593-5p	Downregulated	ICAM-1	Cell proliferation, migration	(98)
miR-650	Upregulated	ING4	Chemo-resistance	(99)
miR-140-5p	Upregulated	ZNF800	Cell proliferation, invasion, migration, apoptosis	(100)
miR-335-5p	Downregulated	CCNB2	Cell proliferation, metastasis	(101)

miR, microRNA.

invasion and metastasis and are related to an unfavorable prognosis and malignancy (50,55,60). However, the role of miRNAs in monitoring prognosis and delaying the progression of LUAD requires further exploration.

miRNA-regulated drug resistance and radiation sensitivity in LUAD. Drug resistance and reduced sensitivity to radiotherapy can lead to treatment failure and tumor recurrence (120,121). miRNAs are considered to induce the corresponding mechanisms in LUAD to improve drug resistance or radiation sensitivity. Cao *et al* (36) found that *miR-192* was significantly upregulated in A549 cells and that LUAD mice carrying *miR192* inhibitors were more sensitive to cisplatin and gemcitabine treatment. Moreover, in the process of improving chemotherapy resistance, *Bcl-2* is upregulated as a key regulatory factor following *miR-192* knockdown (36). Thus, *miR-192* may be a potential target for LUAD chemotherapy. Another miRNA, *miRNA-134*, has been shown to be associated with multiple-drug resistance in LUAD. *MiR-134* has been reported to be significantly downregulated in cisplatin-resistant LUAD cells. Further studies have shown that *miR-134* overexpression enhances the sensitivity of LUAD cells to vincristine and 5-fluorouracil (51). Yuan *et al* (40) confirmed that the upregulation of *miR-195-5p* promotes the expression of Bax and reduces the expression of cyclin D1 and Bcl-2 in A549 and PC9 cells exposed to ionizing radiation. This result indicated

that *miR-195-5p* enhanced the radiosensitivity of LUAD cells by promoting apoptosis (40). In summary, different miRNAs participate in LUAD progression by influencing the downstream target genes. They play an important role in the different phenotypes of LUAD.

3. miRNA-mediated targeting of specific signaling pathways in LUAD

miRNAs play an undeniable role in LUAD, yet, the specific molecular mechanism remains controversial. Generally, these molecules regulate tumor development by targeting downstream genes in multiple signaling pathways (122) (Table II).

AKT signaling pathway. Akt, also known as protein kinase B, is a key medium for GF-induced cell survival (164). Upregulation of Akt activity has been observed in numerous cancers. The interaction between tumor suppressors and tumor-promoting factors in the Akt pathway leads to proliferation, differentiation and inhibition of tumor cell apoptosis (165). The Akt pathway mediates by transporting signals from upstream regulatory proteins (such as PTEN and PI3K) to downstream effector proteins (MDM2 and FOXO). Subsequently, these effectors intersect with numerous other compensatory signaling pathways (166). Furthermore, miRNAs impact tumor progression by interfering with the expression of related genes in the Akt pathway (167). The roles of miRNAs in LUAD progression via the Akt pathway were summarized.

Downregulation of *miR-382-3p* has been shown to contribute to LUAD carcinogenesis. Fang *et al* (128) found that *miR-382-3p* inhibition promotes proliferation and inhibits apoptosis in LUAD cells by mediating *SAE1*, which is considered a key member of the SUMO activation complex. The aforementioned study further verified that upregulation of SAE1 increases SUMO1 and pAkt protein levels. In summary, low *miR-382-3p* expression promotes LUAD progression by promoting SUMO protein modification and Akt phosphorylation.

MiR-200 is considered to promote cancer cell growth via the PI3K/Akt pathway, with FOG2 as its downstream target. However, the FOG2 knockdown had almost no effect on Akt activation. Guo *et al* (140) confirmed that the activation of Akt by miR-200 was accompanied by the inactivation of p70S6K and significant upregulation of IRS-1, which is considered a substrate of p70S6K. More importantly, the knockdown of IRS-1 inhibited Akt phosphorylation, indicating that miR-200 activates Akt via IRS-1.

Similarly, *miR-381* and *miR-409-3p* inhibited proliferation and reduced invasion and migration by regulating the Akt signaling pathway (147,149). Notably, He *et al* (125) found that *miR-3613-5p* acts as an intermediate hub, promoting LUAD progression. The upregulation of *miR-3613-5p* was mediated by RELA as a subunit of nuclear factor-kB (NF-kB) through JUN. Subsequently, *miR-3613-5p* stimulates the Akt/MAPK pathway via NR5A2. In addition, the phosphorylation of Akt1 and MAPK3/1 jointly activates RELA. From this, it could be observed that a RELA/JUN/miR-3613-5p/NR5A2/Akt/MAPK forward feedback loop had been established in the progress of LUAD. Therefore, the pathway mediated by a miRNA in LUAD is not unique and includes multiple overlapping pathways and upstream and downstream pathways forming feedback loops.

STAT3 signaling pathway. Signal transducer and activator of transcription (STAT) proteins are a family of cytoplasmic transcription factors that include STAT5a, STAT4, and STAT3 that regulate numerous signaling pathways. STAT3 is associated with diverse biological processes, including cell proliferation, apoptosis and differentiation (168). Lv *et al* (143) found that *miR-320a* not only regulates STAT3 but also affects its related signals, such as Bcl-2, Bax and Caspase8 to suppress the proliferation and metastasis of LUAD *in vivo* and *in vitro*. It is well known that certain cytokines, such as interleukin-6 (IL-6), bind to corresponding receptors on the cell membrane to activate the JAK2-STAT3 signaling pathway (169). *MiR-204* and *miR-425* were based on this mechanism to suppress the malignant biological behavior of LUAD (141,151). In addition, Xu *et al* (162) confirmed from another perspective that *miR-30e-5p* targets the upregulation of *USP22* and mediates the Sirt1/JAK2/STAT3 pathway, which also inhibits LUAD.

Wnt signaling pathway. The Wnt pathway is a critical signaling cascade in cancer. Abnormal Wnt signaling is observed in numerous cancers, including LUAD. The Wnt signaling pathway mainly affects the stability, migration and immune escape of cancer stem cells (170). Additionally, signaling pathways, such as the Wnt and Notch pathways, typically form a network within cells to jointly regulate tumor progression (171). *MiR-1275* has been reported to be significantly upregulated in LUAD. This trend increased the expression of β-catenin in the Wnt pathway and NICD in the Notch pathway. This miRNA also directly targets and inhibits negative regulatory factors, such as GSK3, RUNX3 and NUMB, in two signaling pathways. This enhances the stem cell phenotype of LUAD cells (123).

Coincidentally, *miR-33b, miR-149*,and *miR-490-3p* inhibit the malignant progression of LUAD through the Wnt/β-catenin signaling pathway. Their main mechanism of action is to reduce catenin expression to inhibit tumor cell proliferation, metastasis and EMT (132,137,153).

MTOR signaling pathway. The mammalian target of rapamycin (mTOR), a serine/threonine kinase, combines hormones, cytokines, nutrients and other factors to regulate biological behaviors including proliferation, differentiation and metabolism of cancer cells (172). It has two different complex forms in cells, mTORC1 and mTORC2, and its C-terminus is homologous to the catalytic domain of phosphatidylinositol kinase (PI3K). mTOR itself does not possess esterase kinase activity but rather has Ser/Thr protein kinase activity (173).

MiR-125 has been shown to inhibit LUAD. It also reduced the p-AKT/AKT ratio, the p-mTOR/mTOR ratio and the expression of RhoA by downregulating TNS1 (154). Additionally, *miR-363-3p* inhibited the proliferation and metastasis of LUAD cells through the mTOR/4EBP-1 and ERK signaling pathways (145). Evidently, the effect of miRNA on cancer often occurs in a multi-pathway and multi-target manner.

LUAD treatment with cisplatin can lead to multiple tolerances in malignant cells. This can cause the cancer cells to lose their sensitivity to drugs, leading to treatment failure.

Table II. Signaling pathways regulated by miRNAs in lung adenocarcinoma.

miRNA	Expression	Target	Signaling pathway	(Refs.)
miR-1275	Upregulated	DKK3, SFRP1, GSK3β, RUNX3 and NUMB	Wnt/β-catenin pathway; Notch signaling pathway	(123)
miR-1307-5p	Upregulated	TRAF3	MAPK/NF-κB pathway	(124)
miR-3613-5p	Upregulated	NR5A2	AKT/MAPK pathway	(125)
miR-6077	Upregulated	GLUT1	Glucose transporter 1 pathway	(126)
miR-6742-5p	Downregulated	FGF8	ERK12/MMP9/MMP2 pathway	(127)
miR-382-3p	Downregulated	SAE1	AKT signaling pathway	(128)
miR-1-3p	Downregulated	E2F8	NF-κB pathway	(129)
miR-21	Upregulated	-	PI3K/AKT/mTOR/HIF-1a Pathway	(130)
miR-31	Upregulated	-	RAS/MAPK pathway	(131)
miR-33b	Downregulated	ZEB1	Wnt/β-catenin signaling pathway	(132)
miR-106a-5p	Upregulated	LKB1	AMPK pathway	(133)
miR-125a-5p	Downregulated	TMPRSS4	NF-κB signaling pathway	(134)
		TIMP-1	p53 signaling pathway	(135)
miR-140-3p	Downregulated	ADAM10	Notch pathway	(136)
miR-149	Downregulated	RAP1B	Wnt/β-catenin pathway	(137)
miR-181	Downregulated	PTEN	PTEN/PI3K/AKT/mTOR signaling pathway	(138)
miR-182-5p	Downregulated	GLI2	Hedgehog signaling pathway	(139)
miR-200	Upregulated	IRS-1	PI3K/AKT signaling pathway	(140)
miR-204	Downregulated	JAK2	JAK2-STAT3 signaling pathway	(141)
miR-206	Downregulated	SMAD3	TGF-β signaling pathway	(142)
miR-320a	Downregulated	STAT3	STAT3 signaling pathway	(143)
miR-345-5p	Downregulated	RhoA	Rho/ROCK pathway	(144)
miR-363-3p	Downregulated	PCNA	mTOR and ERK signal pathway	(145)
miR-365	Upregulated	USP33	USP33/SLIT2/ROBO1 signalling pathway	(146)
miR-381	Downregulated	LMO3	PI3K/Akt signaling pathway	(147)
miR-383	Downregulated	RBM24	NF-κB signaling pathway	(148)
miR-409-3p	Downregulated	c-Met	Akt signaling pathway	(149)
miR-423-3p	Upregulated	CYBRD1	FAK signaling pathway	(150)
miR-425	Downregulated	ADAM9	IL-6/STAT3 signaling pathway	(151)
miR-451	Downregulated	c-Myc	c-Myc/ERK/GSK-3b signalling pathway	(152)
miR-490-3p	Downregulated	-	Wnt/β-catenin signaling pathway	(153)
miR-152	Downregulated	TNS1	Akt/mTOR/RhoA pathway	(154)
miR-520e	Downregulated	Zbtb7a	Wnt signaling pathway	(155)
miR-148b	Downregulated	ALCAM	NF-κB signaling pathway	(156)
miR-1258	Downregulated	GRB2	GRB2/Ras/Erk pathway	(157)
miR-25	Upregulated	LATS2	LATS2/YAP signaling pathway	(158)
	Upregulated	KLF4	ERK signaling pathway	(159)
miR-103a	Downregulated	OTUB1	Hippo signaling pathway	(160)
miR-150	Upregulated	SIRT2	Sirt2/JMJD2A signaling pathway	(161)
miR-30e-5p	Downregulated	USP22	Sirt1/JAK/STAT3 signaling pathway	(162)
miR-132	Downregulated	-	TGFβ1/Smad2 signaling pathway	(163)

-, not mentioned; miR, microRNA.

Cisplatin resistance is a major bottleneck in the treatment of LUAD (174). However, some studies have confirmed that miRNAs affect cisplatin resistance in LUAD through the mTOR signaling pathway. Liu *et al* (138) reported that the overexpression of *miR-181* in A549/DDP cells (a LUAD drug-resistant cell line) promoted autophagy and upregulated the expression of LC3 and AGT5 proteins through the PTEN/PI3K/AKT/mTOR signaling pathway. Additionally,

downregulation of *miR-21* in A549/DDP cells slowed the loss of glucose and the production of pyruvic acid and lactic acid, which promoted the expression of apoptosis-related proteins. This process inhibits glucose metabolism and promotes cell death via the PI3K/AKT/mTOR/HIF-1a pathway (130).

NF-κB signaling pathway. The NF-kB is not a single gene but a family of transcription factors involved in multiple biological processes (175). This signaling pathway not only participates in inflammation and immune response but also plays an important role in the occurrence and development of tumors (176).

Lin (129) reported that miR-1-3p binds to the promoter region of E2F8, thereby inhibiting the malignant phenotype of LUAD cells. During this process, upregulated miR-1-3p significantly negatively regulated NF-κB and STAT3 protein phosphorylation expression (129). MiR-125a-5p had an effect similar to that of miR-1-3p, except that its downstream target was replaced with TMPRSS4. After enhancing miR-125a-5p expression, the expression of IκBκ and cytoplasmic NF-κB was significantly increased, accompanied by a marked decrease in the expression of nuclear NF-κB and p-IκB. Therefore, miR-125a-5p inhibited LUAD by inactivating the NF-κB signaling pathway (134). Similarly, overexpression of miR-148b and miR-383 both inhibited the phosphorylation of p65 and IkBa proteins, leading to the inactivation of the NF-κB signaling pathway. This process suppresses LUAD progression and improves sensitivity to chemotherapy (148,156).

MAPK signaling pathway. The mitogen-activated protein kinase (MAPK) signaling pathway plays an important role in proliferation, differentiation and inflammation-related signaling pathways. It contains four branches, of which the main substrates are extracellular signal-related kinase (ERK) and Jun amino terminal kinase (JNK) (177). Among these, the MAPK/ERK signaling pathway has been associated with tumor-related malignant phenotypes such as cell proliferation and apoptosis (178).

MiR-6742-5p, *miR-363-3p*, *miR-451* and *miR-1258* are expressed at low levels in LUAD and inhibit cell proliferation. Mechanistically, they reduced the phosphorylation of the ERK1/2 protein through the ERK pathway, which is considered a classic branch of the MAPK signaling pathway (127,145,152,157). By contrast, *miR-1307-5p* and *miR-25* participated in the regulation of LUAD as oncogenes through the ERK signaling pathway (127,159).

Other signaling pathways involved in LUAD. Numerous signaling pathways are involved in LUAD tumor regulation, with numerous miRNAs associated with these pathways. Ma *et al* (126) found that *miR-6077* targeted GLUT1 (glucose transporter 1) and inhibited glucose absorption and lactate production after its upregulation. By mediating the glucose transport pathway, *miR-6077* increased the sensitivity of LUAD cells to alotinib (126). Other miRNAs, such as *miR-106a-5p*, were upregulated in LUAD, and it has been shown to suppress the phosphorylation of AMPK and TSC2 proteins, while upregulating the phosphorylation of mTOR. This change promotes the proliferation and autophagy of tumor cells (133). Ghoshal-Gupta *et al* (135) showed that *miR-125a-5p* regulates apoptosis in LUAD cells by upregulating the p53 protein and altering the expression of other related apoptotic proteins, such as Bcl-2 and BAX. There are several additional examples. *MiR-140-3p* enhanced the sensitivity of LUAD cells to antitumor drugs by suppressing the Notch signaling pathway, and *miR-182-5p* plays a similar role through the Hedgehog pathway (136,139). Additionally, TGF β, Hippo, and YAP signaling pathways participated in the regulation of LUAD (142,158,160).

4. Interactions of lncRNA and circRNA with miRNA in LUAD

Recently, competing endogenous RNAs (ceRNAs) have garnered significant research interest as they represent a novel regulatory mechanism between RNAs, rather than representing a distinct type RNA (179). This theory reveals the presence of miRNA response elements (MREs) not only on mRNA but also on lncRNAs and circRNAs (180). Therefore, mRNA, lncRNAs and circRNAs compete with miRNAs to form complex regulatory networks that affect gene expression. Some lncRNAs and circRNAs interact with miRNAs and subsequently affect LUAD progression (Tables III and IV).

Yang *et al* (181) found that *linc00483* is highly expressed in LUAD and positively correlated with poor prognosis. Moreover, it acted as a sponge for *miR-204-3p* in the cytoplasm and regulated ETS1. Another study revealed that HMMR-AS1 plays an important role as a ceRNA in the proliferation and metastasis of LUAD, which regulates the expression of SIRT6 through sponging *miR-138* (183). Chen *et al* (184) demonstrated that HOXA11-AS suppresses the expression of *miR-148b-3p* by binding to its MREs. Subsequently, PKM2 expression is indirectly upregulated and plays a role in glycolysis in cancer cells (184). Numerous miRNAs, such as *Linc00520* and *Linc01833*, are highly expressed in LUAD. They mainly promote cancer cells via the lncRNA/miRNA/mRNA axis (186-193,195). Indeed, lncRNAs exhibit inhibitory effects on cancer phenotypes in LUAD. *Linc01089* is significantly underexpressed in LUAD and competitively binds to miR-301b-3p as a ceRNA. Moreover, *miR-301b-3p* interacted with STARD13, contributing to the proliferation and metastasis of LUAD (183). Recently, Liu *et al* (193) found that SGMS1-AS1 regulates MYLI9 through the competitive isolation of *miR-106a-5p*. A rescue experiment revealed that *MYLI9* overexpression or *miR-106a-5p* inhibition offset the regulatory effect of *SGMS1-AS1* silencing in LUAD cells (194).

Furthermore, multiple studies have confirmed that circRNAs regulate gene expression by suppressing miRNA activity (206). *Circle_ 0006427* was significantly localized in the cytoplasm and was positively regulated by *DKK1* through competitive sponging of *miR-6783-3p* in LUAD cells (195). Huang *et al* (199) reported that the overexpression of *circ_000881* slowed the malignant phenotypes of LUAD cells. Furthermore, *circRNA_000881* acts as a sponge for *miR-665* and indirectly regulates the downstream target gene *PRICKLE2* (199). Similarly, *circ_0129047* and *circ-MTO1* play similar roles as tumor suppressors in LUAD (201,202). Numerous circRNAs act as cancer promoters in LUAD. For example, *circ-CAMK2A* was not only significantly upregulated in LUAD but was also positively correlated

Table III. Interaction between lncRNAs and miRNAs in lung adenocarcinoma.

lncRNA	Expression	miRNA	Expression	Target	(Refs.)
Linc00483	Upregulated	miR-204-3p	Downregulated	ETS1	(181)
Linc01089	Downregulated	miR-301b-3p	Upregulated	STARD13	(182)
HMMR-AS1	Upregulated	miR-138	Downregulated	Sirt6	(183)
HOXA11-AS	Upregulated	miR-148b-3p	Downregulated	PKM2	(184)
Linc00520	Upregulated	miR-1252	Downregulated	FOXR2	(185)
Linc01833	Upregulated	miR-519e-3p	Downregulated	S100A4	(186)
DGCR5	Upregulated	miR-22-3p	Downregulated	-	(187)
AC009948.5	Upregulated	miR-186-5p	Downregulated	NCAPG2	(188)
FAM201A	Upregulated	miR-7515	Downregulated	GLO1	(189)
Linc00960	Upregulated	miR-124a	Downregulated	SphK1	(190)
GLIDR	Upregulated	miR-1270	Downregulated	TCF12	(191)
TMPO-AS1	Upregulated	miR-383-5p	Downregulated	-	(192)
SGMS1-AS1	Downregulated	miR-106a-5p	Upregulated	MYLIP	(193)
Linc00346	Upregulated	miR-30c-2-3p	Downregulated	MYBL2	(194)

lncRNA, long non-coding RNA; miR, microRNA; -, not mentioned.

Table IV. Interaction between circRNAs and miRNAs in lung adenocarcinoma.

circRNA	Expression	miRNA	Expression	Target	(Refs.)
circ_0006427	Downregulated	miR-6783-3p	Upregulated	DKK1	(195)
circ-CAMK2A	Upregulated	miR-615-5p	Downregulated	FN1	(196)
circ_0020850	Upregulated	miR-326	Downregulated	BECN1	(197)
circ_0007142	Upregulated	miR-186	Downregulated	FOXK1	(198)
circ_000881	Downregulated	miR-665	Upregulated	PRICKLE2	(199)
circ_0001998	Upregulated	miR-145	Downregulated	-	(200)
circ_0129047	Downregulated	miR-375	Upregulated	ACVRL1	(201)
circ-MTO1	Downregulated	miR-17	Upregulated	QKI-5	(202)
circ_0020123	Upregulated	miR-1283	Downregulated	PDZD8	(203)
circ_0001588	Upregulated	miR-524-3p	Downregulated	NACC1	(204)
circ_0072088	Upregulated	miR-1261	Downregulated	PIK3CA	(205)

-, not mentioned; circRNA, circular RNA; miR, microRNA.

with an unfavorable prognosis. It upregulates the expression of fibronectin 1 by competitively binding to *miR-615-5p*, thereby enhancing the expression of *MMP9* and *MMP2* and promoting LUAD progression (196). In summary, the circRNA-miRNA-mRNA axis plays a crucial role in LUAD (197,198,200,203-205).

5. Limitations and outlook

However, these experiments also have certain limitations. Firstly, in the article, the approach to revealing the mechanism is relatively singular. It is nothing more than verification at the tissue, cell and animal levels, and further verification through functional gene experiments and phenotype rescue experiments is required. Secondly, during experimental verification, the number of cell line types and tissue samples is relatively small. Thirdly, the current research on miRNAs remians in the basic experimental stage, and how to transition to clinical practice is an urgent issue that needs to be solved.

At present, although numerous miRNAs have been proven to have promoting or inhibiting effects on LUAD, the manipulation of miRNAs has not been translated into practical clinical treatment strategies. The reasons for this are multifaceted. Firstly, numerous miRNAs regulate tumor progression through different target genes and signaling pathways. Therefore, interfering with a single miRNA cannot fundamentally treat LUAD. Correspondingly, a method or drug that can alter the regulatory network targeting miRNAs should be developped. Secondly, the reagents required for overexpression or low expression of miRNAs in basic experiments are cytotoxic. In actual clinical treatment, this is

clearly unacceptable. Thirdly, even if drugs that can interfere with miRNAs while being non-toxic are obtained, how to efficiently and safely enter the human organism remains a challenging issue.

6. Conclusions

Emerging evidence suggests that miRNAs are involved in the regulation of LUAD by degrading or silencing downstream target genes at the post-transcriptional level. miRNAs have been shown to regulate multiple malignant biological phenotypes of LUAD through multiple signaling pathways. The present review systematically summarized the roles of abnormally expressed miRNAs in LUAD and their related signaling pathways.

Research findings suggest that miRNAs hold promise as potential biomarkers of LUAD, and the signaling pathways that they influence could offer innovative targets for LUAD treatment. The interactions between ceRNAs and miRNAs present a novel mechanism for LUAD development. The lncRNA or circRNA/miRNA/mRNA axis has emerged as a major focus in cancer research. Continued investigation is likely to unveil additional miRNA-mediated signaling pathways and therapeutic targets for LUAD, enhancing diagnosis and treatment approaches for this disease.

However, basic research is not equivalent to clinical application. There are still numerous urgent problems to be solved in the treatment of LUAD using miRNAs. For example, there is a lack of effective means for overall intervention in miRNAs-regulatory networks. Meanwhile, drugs that interfere with miRNAs need to be proven to be effective and safe. These practical problems not only pose challenges, but also point in the direction of progress.

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Authors' contributions

JL and FZ wrote the manuscript. YW and JW reviewed the article. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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