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Review

MicroRNAs in lung cancer: their role in tumor progression, biomarkers, diagnostic, prognostic, and therapeutic relevance

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Abstract

MicroRNAs (miRNAs) are a class of small non-coding RNAs which are associated with post-transcriptional regulation of gene expression. Dysfunction or aberrant expression of miRNAs is predominant in various malignancies including lung cancer. Lung cancer is one of the commonest causes of cancer-related death worldwide, with a five-year survival of only 10–20%. The present review summarizes the current understanding of the role of miRNAs in the development and progression of human lung cancer and their therapeutic potential. Also, we briefly discuss the canonical biogenetic pathway of miRNAs followed by a detailed illustration on how miRNAs regulate human lung cancer progression in various ways. Furthermore, we focus on how miRNAs contribute to the crosstalk between cancer cells and different cells in the tumor microenvironment in the context of lung cancer. Finally, we illustrate how different miRNAs are used as a prognostic and diagnostic biomarker for lung cancer and the ongoing miRNA-associated clinical trials. In conclusion, we discuss how targeting miRNAs can be a potential therapeutic means in the treatment of human lung cancer.

Keywords MicroRNAs · Lung cancer · Tumor microenvironment · Lung cancer therapy · Biomarkers

Abbreviations

RNase III	Ribonuclease III
SMAD	Suppressor of mothers against decapentaplegic
E2F3	E2F transcription factor 3
MDM2	Murine double minute 2
HMGA2	High-mobility Group AT-hook 2
mTOR	Mammalian target of rapamycin
ZEB	Zinc Finger E-Box Binding Homeobox
LATS2	Large tumor suppressor kinase 2
β-TrCP	Beta-transducin repeat-containing protein
NDR2	Nuclear Dbf2-related (NDR) kinase 2
LZTS1	Leucine zipper putative tumor suppressor 1
DNMT	De Novo methyltransferases

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MMP-2	Matrix metalloproteinase 2
VEGF	Vascular endothelial growth factor
PHD	Plant homeodomain
GAX	Growth arrest-specific homeobox gene
TFAP4	Transcription factor AP-4
CDK8	Cyclin dependent kinase 8
BCL2L2	B-cell leukemia/lymphoma 2-like protein 2
GLUT1	Glucose transporter 1
MVs	Microvesicles
T_{reg}	T-regulatory
LDHA	Lactate dehydrogenase-A
FIH	Factor inhibiting HIF
HIF	Hypoxia-inducible factor
ATP	Adenosine triphosphate
PD-L1	Programmed death ligand 1
PD1	Programmed cell death protein 1
NR5A2	Nuclear receptor subfamily 5 group A member 2
PTEN	Phosphatase and tensin homolog
STAT	Signal transducer and activator of transcription
TME	Tumor microenvironment
ECM	Extracellular matrix
CAF	Cancer-associated fibroblast
TAM	Tumor-associated macrophage
TIL	Tumor-infiltrating lymphocyte
CXCL12	C-X-C motif chemokine ligand 12
SDF-1	Stromal cell-derived factor 1
PPARγ	Peroxisome proliferator-activated receptor gamma
ZO-1	Zonula Occludens 1
eNOS	Endothelial nitric oxide synthase
EMT	Epithelial to mesenchymal transition
FOXM1	Forkhead box M1
NSCLC	Non-small-cell lung cancer
Twist1	Twist-related protein 1
Wnt	Wingless/integrated
TGFβ	Transforming growth factor beta
FOXO3A	Forkhead box O3A
TP53INP1	Tumor protein P53 inducible nuclear protein 1
EGFR	Extracellular growth factor receptor
TKI	Tyrosine kinase inhibitor
PI3K	Phosphoinositide 3 kinase
JAK	Janus kinase
Ras	Rat sarcoma virus
Raf	Rapidly accelerated fibrosarcoma
MAPK	Mitogen-activated protein kinase
AMO	Antisense morpholino
FAK	Focal adhesion kinase
MEK	Mitogen-activated protein kinase kinase
ERK	Extracellular signal-regulated kinase
SphK2	Sphingosine kinase 2
LUAD	Lung adenocarcinoma

1 Introduction

Lung cancer is one of the leading causes of cancer-related death in the United States. In the year 2023, approximately 1,15,000 new cases and 60,000 deaths are estimated in the US, representing ~13% new cases and 21% death among all types of cancer in both males and females [1]. Lung cancer can be classified into two major groups by histology examination, small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC), the latter being the predominant one, comprising > 80% of the total lung cancer. NSCLC is further subdivided into large-cell carcinoma, adenocarcinoma, and squamous cell carcinoma [2]. The prognosis of lung cancer is poor as patients are often diagnosed at advanced stages, e.g., > 60% of lung cancer patients are diagnosed at stage III or IV before any treatment [3]. As a result, survivability of lung cancer becomes very less, 16.8% in five years and < 5% with metastatic phenotype [4]. Therefore, not only in genetic aspect, but epigenetic understanding of lung cancer tumorigenesis also becomes indispensable in improving diagnosis.

MicroRNAs (miRNAs) are a class of small non-coding RNAs, ~20–25 nucleotides long, which alters post-transcriptional gene expression by binding to the target mRNAs at complementary sequences resulting in the inhibition of mRNA translation and degradation of the target mRNAs [5–9]. The biogenesis of miRNAs is comprised of two pathways: (1) Canonical pathway and (2) non-canonical pathway. The present review will preferentially undergo detailed understanding of the canonical pathway, the most predominant pathway of miRNA biogenesis (Fig. 1). The canonical pathway is initiated by RNA polymerase II to transcribe ~100 nucleotides long precursor miRNAs (pri-miRNAs) [5]. In the nucleus, the pri-miRNAs are processed by an RNase III enzyme, Drosha and a double-stranded RNA (dsRNA)-binding protein, Pasha (also known as DiGeorge Syndrome critical region gene 8, DGCR8) to generate ~70 nucleotides long pre-miRNAs [5]. Pre-miRNAs are readily transported into the cytoplasm by an energy-driven process, mediated by Ran GTP-dependent dsRNA-binding protein, exportin-5 (XPO-5) [5]. In the cytoplasm, the pre-miRNAs are further processed by another RNase III enzyme, Dicer to generate ~22 nucleotides long mature miRNA:miRNA duplexes [5]. Then, another energy-driven process loads both mature miRNA strands into Argonaute (AGO) protein. The AGO preferentially takes the strand with lower 5′ stability or strand with 'U' at nucleotide 1 at the 5′ end, called mature miRNA strand whereas the other strand, the passenger strand is subsequently degraded by the AGO [5].

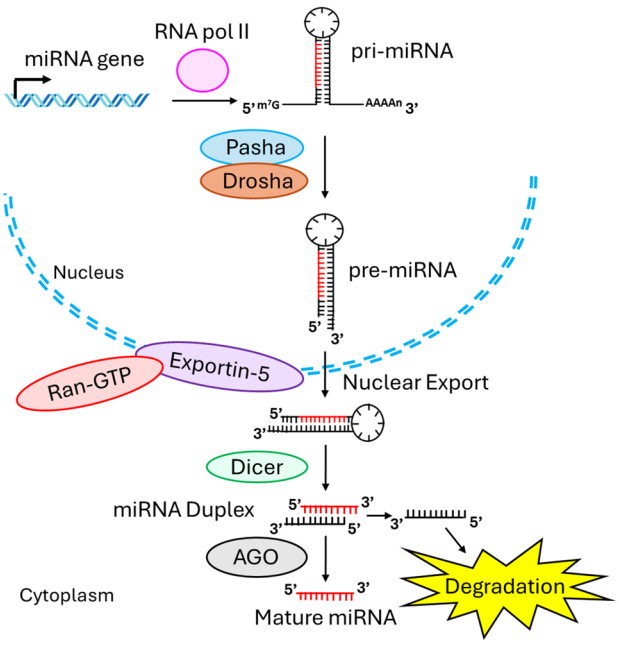

Fig. 1 The canonical pathway of miRNAs biogenesis. miRNAs are transcribed from the genome in the nucleus by RNA Pol II to produce pri-miRNAs, which are processed by Pasha-Drosha to generate pre-miRNAs. Pre-miRNAs are readily transported via Ran-GTP-Exportin-5 into the cytoplasm. In the cytoplasm, pre-miRNAs are further processed by Dicer to form the miRNA: miRNA duplex. miRNA duplex then binds to AGO, which further processes the duplex to generate one mature miRNA strand while degrading the other strand. *pol II* polymerase II, *miRNA* microRNA, *Drosha* Drosha ribonuclease III, *Pasha* partner of Drosha, *Ran* RAs-related nuclear protein, *AGO* Argonaute

2 Factors influencing lung cancer pathogenesis

Risk factors for lung cancer can be categorized into genetic- and environmental factors. Emerging evidence indicates that approximately 8–14% of lung cancer are caused by the genetic aberrations [10]. Defects in genetic materials often result in impaired normal cellular functions such as cell proliferation, apoptosis, DNA repair etc., often observed in the context of lung cancer [11]. For example, 10–30% lung adenocarcinomas are caused by the mutations in proto-oncogene, K-Ras [12]. EGFR mutations are quite common in the pathogenesis of human lung carcinomas [13]. Dysregulation of p53 expression, a tumor suppressor gene, is also observed in 60–70% lung cancer [14, 15]. Moreover, mutation or altered expression of BCL2 gene is also shown to influence the development of human lung cancer [16, 17]. Other than the genetic causes, environmental factors such as smoking, air pollution, radon gas, asbestos exposure etc. also induce the development of human lung cancer [18–21]. For example, asbestos exposure leads to the up-regulation of miR-21 expression which may promote lung carcinogenesis via targeting programmed cell death 4 (Pdcd4) and reversion-inducing-cysteine-rich protein with kazal motifs (Reck) [22]. The following section also provides a few examples where both genetic- and environmental factors influence lung cancer pathogenesis, associated with miRNA regulation.

3 miRNAs in lung cancer development and progression

A growing body of evidence indicates that miRNAs play a crucial role in the development and progression of human lung cancer. miRNAs not only modulate the proliferation, growth, metastasis, and angiogenesis of lung cancer but also are shown to influence the replicative immortality, apoptosis, immune evasion, and metabolism of the cancer cells. How different miRNA molecules influence different properties of lung tumors, either aiding in the development and progression of tumors or elimination of tumors from the system, is summarized in Table 1.

3.1 Proliferation

Epidermal growth factor receptor (EGFR) signaling, via the downstream activation of Ras-Raf-MEK-ERK and PI3K-AKT-mTOR pathways plays a pivotal role in the development and progression of lung cancer. The tumor suppressive miRNA, miR-218-5p, is known to inhibit proliferation and migration of lung cancer cells via directly targeting EGFR [23]. In a murine xenograft model, the downregulation of EGFR was found to be mediated by miR-218-5p [23]. The expression of miR-218-5p in NSCLC tissues is also shown to be inversely correlated with EGFR proteins [23]. Another miRNA, miR-134 also targets EGFR and, thereby, suppressing proliferation of NSCLC cells [24]. miR-338-3p again targets sphingosine kinase 2 (SphK2) and inhibits proliferation as well as promotes apoptosis of NSCLC cells [25]. In a murine xenograft model, the downregulation of EGFR was found to be mediated by miR-218-5p [23]. The expression of miR-218-5p in NSCLC tissues is also shown to be inversely correlated with EGFR proteins [23]. On the other hand, miR-3613-5p plays an oncogenic role in lung adenocarcinoma (LUAD) and promotes cell proliferation via directly targeting NR5A2 and subsequent activation of AKT-MAPK pathway. Thus miR-3613-5p acts as a key regulator of the positive feedback loop between the NF-κB/RELA and AKT/MAPK pathways [26]. Similarly, miR-21-5p enhances lung cancer cells migration, invasion and proliferation via targeting SMAD7 [27]. In a recent study, Zhang et al. have demonstrated that smoking induces the expression of miR-9-5p which is positively correlated with cell proliferation and migration, hence may contribute to NSCLC pathogenesis [28]. Moreover, exposure of PM2.5 (particulate matter with an aerodynamic diameter < 2.5 μm) to human bronchial epithelial cells induces miR-155 expression which promotes cell proliferation by targeting SOCS1 and activation of STAT3 signaling pathway [29].

3.2 Growth

miR-15a and miR-16, which targets Cyclin D1, D2 and E1 in NSCLC cells thereby causing cell-cycle arrest and reducing cell growth, are significantly down-regulated in NSCLC cells [30]. miR-449a expression is shown to be significantly down-regulated in lung cancer tissues which cause cell-cycle arrest and induces cell senescence via directly targeting E2F3 [31]. miR-641 also down regulated in lung cancer tissues while, overexpression of miR-641 decreases MDM2 expression and increases p53 expression and increase apoptosis in lung cancer cells [32]. Moreover, let-7 g acts as

Table 1 Different miRNAs with their targets, phenotypic effects and functions in the development and progression of human lung cancer

Effect of phenotype/s	miRNA	Target/s	Function/s	Reference/s
Proliferation	miR-218-5p	EGFR	Inhibits proliferation and migration of lung cancer cells	[23]
	miR-134	EGFR	Inhibits proliferation of NSCLC cells	[24]
	miR-338-3p	SphK2	Inhibits proliferation and induces apoptosis of NSCLC cells	[25]
	miR-3613-5p	NR5A2	Promotes proliferation of LUAD cells	[26]
	miR-21-5p	SMAD7	Promotes proliferation, migration and invasion of lung cancer cells	[27]
	miR-9-5p	–	Smoking induces miR-9-5p expression, promoting migration and proliferation of NSCLC	[28]
	miR-155	SOCS1	PM2.5 exposure induced miR155 promotes lung cancer proliferation	[29]
Growth	miR-15a/16	Cyclin D1, D2, E1	Arrests cell cycle in NSCLC cells and prevents cell growth	[30]
	miR-449a	E2F3	Arrests cell-cycle and induces senescence in lung cancer	[31]
	miR-641	MDM2	Induces apoptosis and prohibits cell growth	[32]
	let-7 g	K-Ras, HMGA2	Suppress the growth of NSCLC tumor	[33]
	miR-1271	mTOR	Inhibits the growth of NSCLC tumor	[34]
	miR-122-5p	p53	Limits tumor growth by inhibiting mevalonate pathway	[35]
Invasion and metastasis	miR-200	ZEB1, ZEB2	Restores E-Cadherin expression in lung cancer cells to reducemotility	[39]
	miR-148a	DNMT1	Suppresses the migration and invasion of lung cancer cells	[40]
	miR-29b	MMP-2, PTEN	Inhibits NSCLC metastasis	[41]
	miR-135b	LATS2, β-TrCP, NDR2, LZTS1	Promotes NSCLC cell migration and invasion in vitro and metastasis in vivo	[42]
	miR-21	PTEN	Induces migration and invasion of NSCLC cells	[43]
	miR-194-3p	p27 kip1	Activate RhoA signaling pathway to inhibit cell migration	[44]
Immortality	miR-29	DNMT3A, 3B	May interfere with telomerase function to reduce cell mortality	[47]
Angiogenesis	miR-200	VEGF	Reduces angiogenesis in lung cancer	[48]
	miR-126 & miR-128	VEGF-A& VEGF-C	Reduces lung cancer angiogenesis	[49, 50]
	miR-494	PTEN	Induces lung cancer angiogenesis	[51]
	miR-23a	PHD1, −2	EVs' carrying miR-23a induce HIF-1α in endothelial cells, inducing angiogenesis	[63]
	miR-141	GAX	Metastatic lung cancer-derived exosomes transfer miR-141 to endothelial cells, leading to enhanced tube formation	[64]
	miR-619-5p	$RCAN_{1.4}$	NSCLC-derived EVs promote angiogenesis via the transfer of miR-619-5p	[65]
Apoptosis	miR-608	TFAP4	Induces apoptosis in NSCLC cells	[66]
	miR-567	CDK8	Induces apoptosis in NSCLC cells	[67]
	miR-1469	STAT5a	Enhances etoposide-induced lung cancer cell apoptosis	[68]
	miR-1284	Myc	Induces apoptosis of lung cancer cells	[69]
	miR-15a	BCL2L2	Promotes apoptosis of NSCLC cells	[70]
	miR-7	BCL2	Promotes apoptosis of lung cancer cells	[71]
Cell metabolism	miR-144	GLUT1	Reduces glucose uptake and lactate production in NSCLC cells	[72]
	miR-199a-5p	GLUT1	Inhibits NSCLC glucose metabolism	[73]
	miR-33b	LDHA	Decrease glucose metabolism in NSCLC	[74]

Table 1 (continued)

Effect of phenotype/s	miRNA	Target/s	Function/s	Reference/s
	miR-124	AKT1/2, GLUT1, HKII	Inhibits glycolysis and energy metabolism	[75]
	miR-31-5p	FIH	Induces HIF-1 function ultimately results in enhanced ATP production	[76]
Immune evasion	miR-34a	PD-L1	Prevents lung cancer immune evasion	[78]
	miR-197	STAT3	Prevents STAT3-induced PD-L1expression in NSCLC cells	[79]
	miR-138-5p	PD-L1,PD-1	miR-138-5p targets PD-L1 and PD-1on NSCLC cells and T-cells, respectively, aiding in killing tumor cells by T-cells	[80]
	miR-4458	STAT3	Inhibits STAT3-dependent PD-L1expression, thereby suppressing NSCLC immune evasion	[81]
	miR-214	PTEN	Lung tumor-derived MVs transport miR-214 to T_{reg} cells, leading to T_{reg} expansion which promotes tumor growth via the release of IL-10	[82]

miR microRNA, *EGFR* epidermal growth factor receptor, *SphK2* sphingosine kinase 2, *NSCLC* non-small cell lung cancer, *NR5A2* nuclear receptor subfamily 5 group A member 2, *LUAD* lung adenocarcinoma, *SMAD7* mothers against decapentaplegic homolog 7, *E2F3* E2F transcription factor 3, *MDM2* mouse double minute 2 homolog, *HMGA2* high-mobility group AT-hook 2, *mTOR* mammalian target of rapamycin, *ZEB* zinc finger E-box-binding homeobox, *LATS2* large tumor suppressor kinase 2, *β-TrCP* beta-transducin repeat-containing protein, *NDR2* nuclear Dbf2-related (NDR) kinase 2, *LZTS1* Leucine zipper putative tumor suppressor 1, *DNMT* DNA methyltransferase, *VEGF* vascular endothelial growth factor, *PTEN* phosphatase and tensin homolog, *PHD* prolyl hydroxylase, *HIF* hypoxia-inducible factor, *GAX* growth arrest-specific homeobox gene, *TFAP4* transcription factor AP-4, *CDK8* cyclin-dependent kinase 8, *BCL2L2* B-cell leukemia/lymphoma 2-like protein 2, *GLUT1* glucose transporter 1, *MVs* microvesicles, T_{reg} *cells* T-regulatory cells, *LDHA* lactate dehydrogenase A, *FIH* factor inhibiting HIF, *ATP* adenosine triphosphate, *STAT* signal transducer and activator of transcription, *PD-L1* programmed death-ligand 1, PD-1 programmed cell death protein 1

a tumor suppressor which down-regulates NSCLC growth by targeting K-Ras and HMGA2 [33]. In let-7 g expressing tumors of mouse xenograft, a significant decrease in K-Ras and HMGA2 is observed and ectopic expression of K-Ras rescues let-7 g-induced tumor suppression [33]. Similarly, the expression of miR-1271 is shown to be down-regulated in NSCLC tumor which suppresses the growth of NSCLC both in vitro and in vivo via targeting mTOR [34]. As an underlying mechanism, the authors have shown that miR-1271 binds to the 3′-UTR of mTOR, leading to the suppression of mTOR translation [34]. Overexpression of miR-1271 downregulates mTOR protein expression and thus retarding NSCLC growth [34]. Again, miR-122-5p is shown to down-regulate the expression of p53, leading to the inhibition of mevalonate pathway, thereby limiting tumor growth [35].

3.3 Invasion and metastasis

Metastasis, the spreading of tumor from the primary site to other areas of the body, is facilitated by enhanced migration and invasiveness of the tumor cells [36]. Epithelial to mesenchymal transition (EMT) is a process in which the cells lose their adhesion properties and increase the motility to facilitate tumor invasion and metastasis [37]. Earlier evidence indicates that coagulation protease factor VIIa, apart from its common role in coagulation [38], promotes EMT via the release of miR-221-enriched MVs, thereby facilitating the growth and metastasis of human breast cancer [7]. miR-200 is shown to target ZEB1 and ZEB2 which are known repressors of the epithelial marker, E-Cadherin, thereby reducing invasion and metastasis of lung cancer cells [39]. Similarly, miR-148a is shown to be under-expressed in lung cancer, which is known for targeting DNMT1, leading to enhanced expression of E-Cadherin and suppression of lung cancer cell migration and invasion [40]. Another study indicates that miR-29b acts as a tumor suppressor miRNA which attenuates NSCLC metastasis via targeting MMP-2 and PTEN [41]. In contrast to the above, miR-135b not only promotes the migration and invasion of NSCLC cells, but also facilitates the metastasis of NSCLC tumor in vivo by targeting multiple molecules of the Hippo signaling pathway such as LATS2, β-TrCP, NDR2, and LZTS1 [42]. Similarly, miR-21 over-expression in NSCLC is observed to be associated with enhanced cell migration and invasion via the down-regulation of PTEN [43]. Exposure of lung cancer with high doses of radon leads to the down-regulation of miR-194-3p expression, thereby up-regulating its target, p27 kip1 levels which trigger the inactivation of RhoA signaling pathway and promotes cell migration [44].

3.4 Replicative immortality

The human telomerase reverse transcriptase (hTERT) is a catalytic subunit of telomerase which essentially adds telomeric repeat sequences to the telomeric ends of the DNA thereby helping the cells to live for successive generations [45]. DNMTs often induce the expression of hTERT [46] and miR-29 family directly targets DNMT3A and DNMT3B in lung cancer cells [47], thereby may regulate hTERT expression and thus act as a tumor suppressor.

3.5 Angiogenesis

miR-200b is known to negatively regulate Vascular endothelial growth factor (VEGF) signaling by targeting VEGF and its receptors Flt-1 and KDR in lung cancer cells and reduce tumor angiogenesis [48]. Other miRNAs such as miR-126 and miR-128 also target VEGF-A and VEGF-C respectively, to decrease lung cancer angiogenesis [49, 50]. On the other hand, miR-494 targets VEGF suppressor, PTEN and induces angiogenesis in lung cancer [51]. Extracellular vesicles (EVs), known to carry bioactive miRNAs [6, 52], play a significant role in the intercellular communication between cells [53–60], therefore are considered as effective biomarkers for cancer progression [61, 62]. EVs from lung cancer cells under hypoxic condition are enriched with miR-23a and the transfer of EVs' miR-23a into endothelial cells results in the downregulation of miR-23a targets, prolyl hydroxylase 1 and 2 (PHD1 and 2) thereby accumulating HIF-1α in endothelial cells to increase angiogenesis. Moreover miR-23a also increase vascular permeability and cancer trans endothelial migration by targeting tight junction proteins ZO-1 and modulates tumor vasculature [63]. Similarly, Wang et al. have shown that metastatic lung cancer-derived exosomes promote tube formation via transporting miR-141 in endothelial cells and down-regulating its target GAX [64]. Moreover, NSCLC-derived EVs are shown to be enriched with miR-619-5p which not only induces proliferation and metastasis of NSCLC cells but also promotes angiogenesis via targeting $RCAN_{1.4}$ [65].

3.6 Apoptosis

miR-608, which is down-regulated in NSCLC tissues, targets TFAP4 and promotes doxorubicin-induced apoptosis in NSCLC cells [66]. miR-567 is shown to target CDK8 in NSCLC cells, thereby inducing apoptosis and decrease cell proliferation [67]. Similarly, etoposide-induced lung cancer apoptosis is enhanced by miR-1469 over-expression which acts via targeting STAT5a [68]. In a similar study by Li et al., lung cancer apoptosis is shown to be facilitated by miR-1284 via targeting Myc [69]. NSCLC apoptosis is also induced by miR-15a over-expression which targets BCL2L2, thereby facilitating tumor suppression [70]. Similarly, miR-7 is shown to target BCL2 upon binding to its 3′ UTR, thereby promoting apoptosis and thus suppressing lung tumor growth [71].

3.7 Cellular metabolism

miR-144 targets GLUT1 in NSCLC cells and lower expression of miR-144 in NSCLC leads to enhanced glucose uptake and lactate production [72]. GLUT1 is also targeted by miR-199a-5p in NSCLC cells, leading to the inhibition of glucose metabolism; hence, a lower miR-199a-5p expression is often observed in NSCLC [73]. Reduced expression of miR-33b in NSCLC tissues is associated with the up-regulation of miR-33b target, LDHA thereby enhancing glucose metabolism [74]. A lower expression of miR-144 is accompanied by an enhanced rate of glycolysis and energy metabolism in NSCLC cells in which miR-144 is shown to act on multiple targets, AKT1/2, GLUT1, and HKII [75]. Overexpression of miR-31-5p in lung cancer cells results in the down-regulation of miR-31-5p target, FIH, thereby removing its inhibitory action on HIF-1 to promote HIF-1-induced expression of glycolytic enzymes resulting in enhanced ATP production through Warburg Effect [76].

3.8 Immune evasion

The tumor cells have an extraordinary capability to evade the host immune system which is predominantly achieved by PD-L1/PD-1 pathway. PD-L1 is expressed on tumor cells, whereas its receptor, PD-1, is found on T-cells. The binding of tumor cell-associated PD-L1 with PD-1 on T-cells induces apoptotic signaling in T-cells, thereby resulting in T-cell death and tumor immune evasion [77]. Down-regulation of PD-L1 targeting miRNAs is often observed in NSCLC tissues. miR-34a directly targets PD-L1 in lung cancer cells, hence inhibiting the tumor immune evasion [78]. Another miRNA, miR-197 indirectly targets PD-L1. miR-197 targets STAT3 in chemo resistant NSCLC cells, thereby resulting in the inhibition of PD-L1 expression (STAT3 binds to the promoter of PD-L1 and promotes its transcriptional activation) [79]. In a similar way, miR-138-5p is shown to down-regulate the expression of PD-L1 and PD-1 on NSCLC cells and T-cells respectively, thereby enhancing the capability of T-cells to kill the tumor cells [80]. The down-regulation of miR-4458 results in the up-regulation of miR-4458 target, STAT3 which further triggers the expression of PD-L1 in NSCLC cells, contributing to tumor immune evasion [81]. Furthermore, lung tumor-derived microvesicles (MVs) are shown to be enriched with miR-214 which targets PTEN in T-regulatory (T_{reg}) cells, leading to T_{reg} expansion [82]. These T_{reg} cells release significant amounts of IL-10 which further promotes tumor growth. Figure 2 briefly illustrates how different miRNAs influence various properties of the lung cancer cell, leading to either progression or inhibition of the tumor.

4 Role of miRNAs in the tumor microenvironment

The tumor microenvironment (TME) is composed of tumor cells and their surrounding milieu, basically consist of extracellular matrix (ECM) and stromal cells [83]. ECM, again comprised of cancer-associated fibroblasts (CAFs), endothelial cells, tumor-associated macrophages (TAMs), tumor-infiltrating lymphocytes (TILs), dendritic cells etc. which all contribute to the tumorigenesis [84]. miRNAs play an important role in regulating the interaction between tumor cells and their surrounding cells [85]. Table 2 also summarizes the function of different miRNAs in the TME.

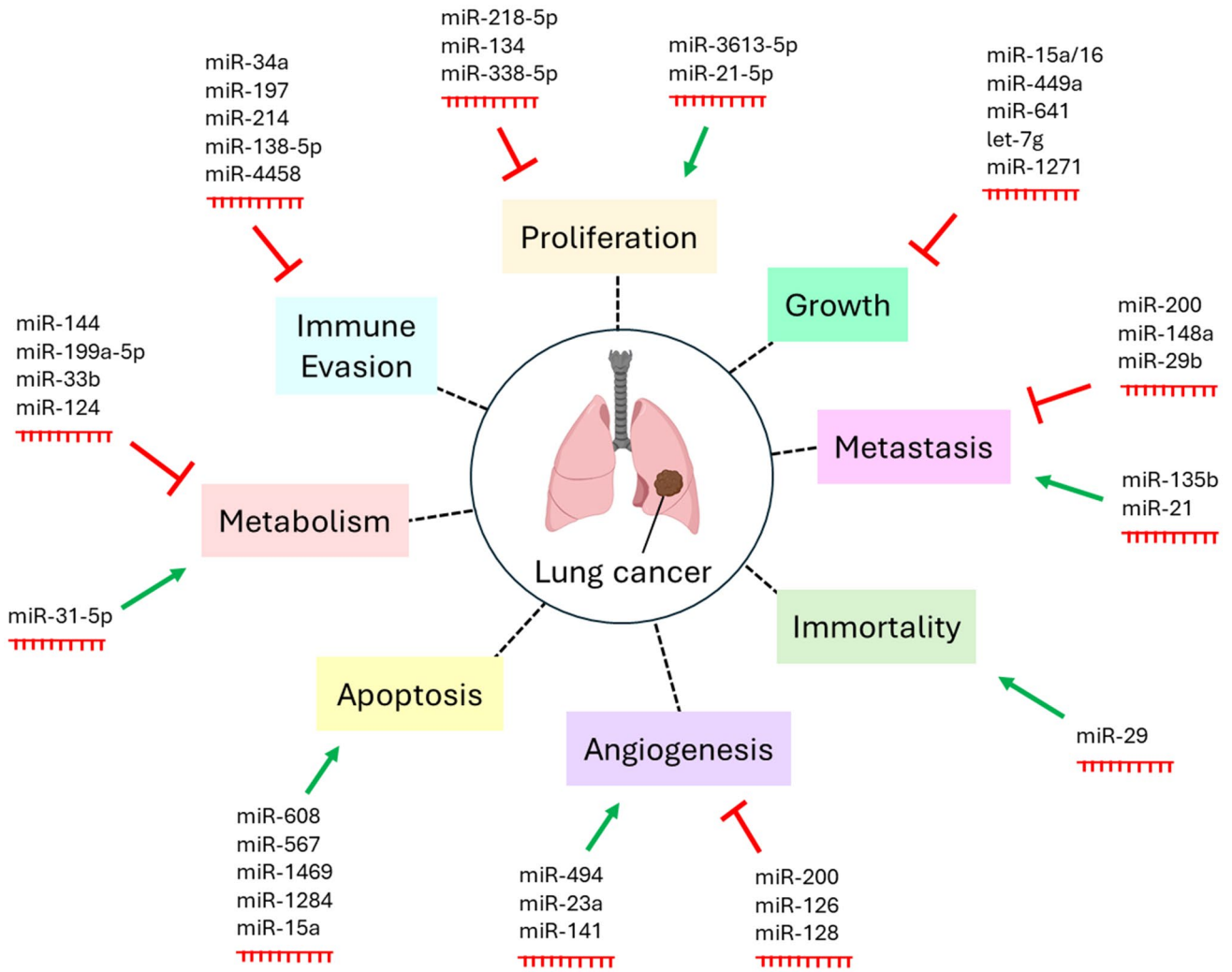

Fig. 2 miRNAs influencing different stages of lung cancer development and progression. miR-218-5p, miR-134 and miR-338-5p inhibit the proliferation of lung cancer whereas, miR-3613-5p and miR-21-5p promote tumor proliferation. miR-15a, miR-449a, miR-641, let-7g, and miR-1271 are shown to inhibit lung tumor growth. miR-200, miR-148a, and miR-29b prevent lung cancer metastasis whereas miR-135b and miR-21 promote it. miR-29 reduces mortality of lung tumors. miR-200, miR-126 and miR-128 are shown to inhibit lung tumor angiogenesis whereas miR-494, miR-23a, and miR-141 promote it. miR-608, miR-567, miR-1469, miR-1284, and miR-15a are known to trigger apoptosis of lung cancer cells. miR-31-5p positively regulates lung tumor metabolism and miR-144, miR-199a-5p, miR-33b, and miR-124 perturb the important metabolic pathways of the tumor cells. On the other hand, miR-34a, miR-197, miR-214, miR-138-5p, and miR-4458 are known for inhibiting immune evasion mechanisms of lung tumor. The green arrows indicate induction, the red reverse 'T' indicates inhibition. *miR* microRNA

4.1 Cancer-associated fibroblasts

The downregulation of miR-101 expression is often observed in CAFs which increases its target, CXCL12 expression, thereby promoting cancer cell proliferation, 3-D spheroid formation, migration and invasion while inhibiting apoptosis [86]. Again, the low level of miR-1 in CAFs is associated with higher expression of its target, stromal cell-derived factor 1 (SDF-1) which promotes lung cancer proliferation and drug resistance [87].

Table 2 The function of different miRNAs in tumor microenvironment

miRNA	Cells of origin	Target	Function	References
miR-101	CAFs	CXCL12	Low miR-101 level in CAFs promote tumor cell proliferation, sphere formation, metastasis and prevents apoptosis	[86]
miR-1	CAFs	SDF-1	Low miR-1 expression in CAFs induce proliferation and drug resistance of cancer cells	[87]
miR-320a	TAMs	STAT4	High miR-320a converts TAMs into M2-macrophages with immunosuppressive functions to promote tumor progression	[88]
miR-130a	TAMs	PPARγ	miR-130a in TAMs induces M2-macrophage formation to promote tumor progression	[89]
miR-23a	Tumor cells	PHD-1, –2, ZO-1	Exosomal miR-23a promote angiogenesis and induces vascular permeability for trans endothelial migration of cancer cells	[63]
miR-494	Tumor cells	PTEN	Promote angiogenesis	[51]
miR-149	NSCLC cells	FOXM1	Induces EMT and metastasis of lung cancer	[90]
miR-33a	NSCLC cells	Twist1	Induces EMT and metastasis of lung cancer	[91]

miR microRNA, *CAF* cancer-associated fibroblast, *CXCL12* C-X-C motif chemokine ligand 12, *SDF-1* stromal cell-derived factor 1, *TAM* tumor-associated macrophage, *STAT4* signal transducer and activator of transcription 4, *PPARγ* peroxisome proliferator-activated receptor gamma, *PHD* prolyl hydroxylase, *ZO-1* zonula occludens 1, *PTEN* phosphatase and tensin homolog, *FOXM1* forkhead box protein M1

4.2 Tumor-associated macrophages (TAMs)

miR-320a targets STAT4 in TAMs which is promoted to an immunosuppressive macrophage M2-like phenotype, thereby contributing to tumorigenesis by increasing cancer cell proliferation, invasion, metastasis, and angiogenesis [88]. Moreover, miR-130a in TAMs targets PPARγ to develop an M2-type macrophages which in turn, target the immune system to promote tumor progression [89].

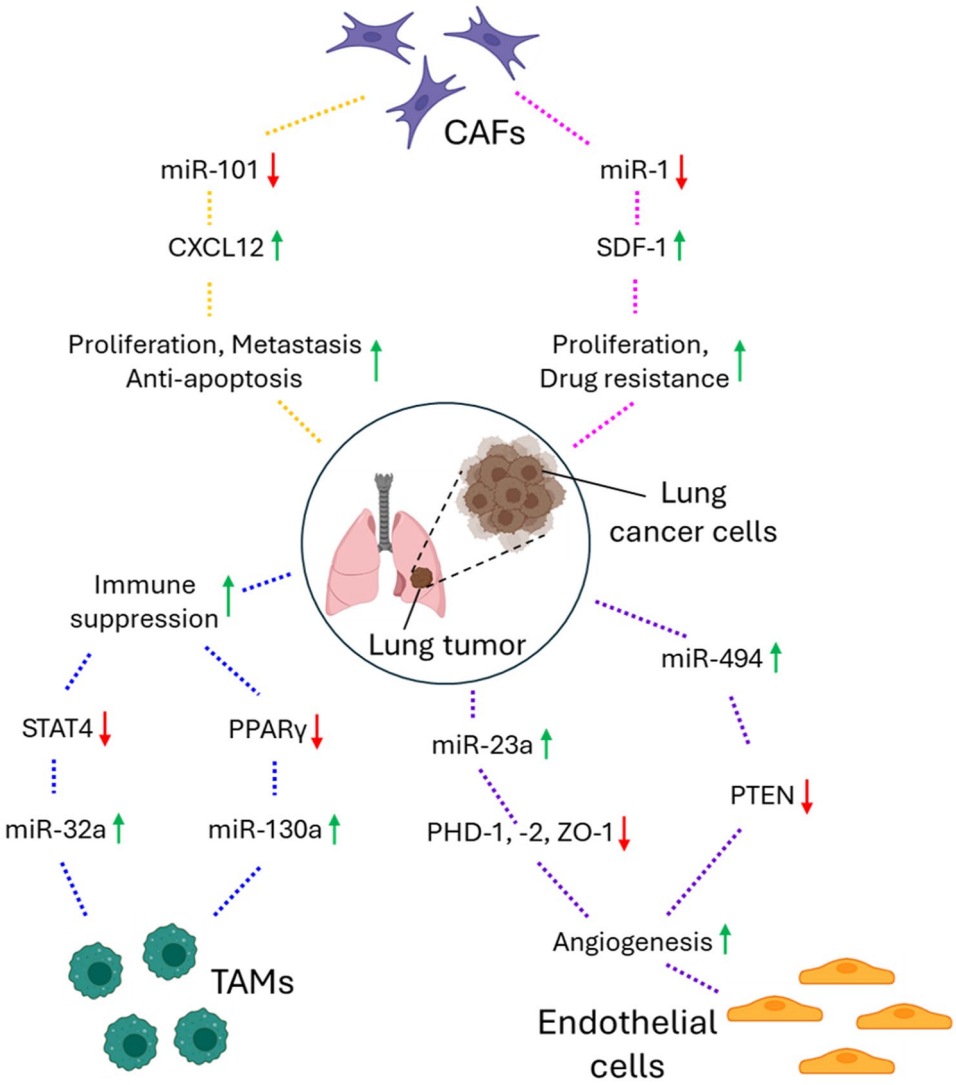

Fig. 3 miRNAs and the crosstalk between lung cancer cells and the cells in TME. Lower expression of miR-101 in CAFs results in the upregulation of its target, CXCL12, leading to the induction of proliferation, metastasis, and anti-apoptosis of lung cancer cells (yellow dotted lines). Again, the downregulation of miR-1 in CAFs is associated with the upregulation of its target, SDF-1 which in turn promotes proliferation and drug resistance of lung tumor cells (pink dotted lines). Higher expression of miR-32a and miR-130a in lung TAMs results in the downregulation of the targets, STAT4 and PPARγ respectively, leading to the induction of immunosuppressive mechanisms (blue dotted lines). Lung tumor cells release miR-23a and miR-494 through exosomes which target PHD-1, −2, ZO-1 and PTEN respectively, in endothelial cells, thereby promoting tumor angiogenesis (violet dotted lines). The green upward arrows indicate upregulation, the red downward arrows indicate downregulation. *miR* microRNA, *CAFs* cancer-associated fibroblasts, *CXCL12* C-X-C motif chemokine ligand 12, *SDF-1* stromal cell-derived factor 1, *TAMs* tumor-associated macrophages, *STAT4* signal transducer and activator of transcription 4, *PPARγ* peroxisome proliferator-activated receptor gamma, *PHD* prolyl hydroxylase, *ZO-1* zonula occludens 1, *PTEN* phosphatase and tensin homolog

4.3 Tumor endothelial cells and angiogenesis

In hypoxic condition, lung tumor cells are shown to release miR-23a via exosomes which not only targets PHD-1 and −2 to promote angiogenesis but also induce barrier permeability and trans endothelial migration of cancer cells via targeting tight junction protein, ZO-1 [63]. miR-494, on the other hand, targets PTEN in endothelial cells, thereby activating AKT/eNOS pathway to promote angiogenesis [51].

4.4 Epithelial to mesenchymal transition (EMT)

The downregulation of miR-149 expression is often observed in NSCLC cells. miR-149 targets Forkhead box M1 (FOXM1) and the down-regulation of miR-149 increases FOXM1 expression, thereby promoting EMT, helping in the metastatic dissemination of cancer [90]. Low level of miR-33a in NSCLC cells is accompanied by the up-regulation of its target, Twist1 expression to promote EMT-associated metastasis of cancer [91]. The miRNAs and the crosstalk between lung tumor cells with the cells in TME are shown in Fig. 3.

5 Role of miRNAs in lung cancer diagnosis and prognosis

miRNAs play a pivotal role in the diagnosis and prognosis of human lung cancer (Table 3). The present section briefly illustrates how miRNAs contribute to lung cancer diagnosis and prognosis.

5.1 miRNAs in lung cancer diagnosis

hsa-miR-205 was exclusively found in NSCLC cells of squamous cell carcinoma [92] whereas miR-124a was limited to adenocarcinoma [93]. Another group observed a higher expression of miR-205, miR-93, miR-221, and miR-30e in squamous cell carcinoma whereas miR-29b, miR-29c, let-7e, miR-100, and miR-125a-5p were shown to be up-regulated in adenocarcinoma [94]. On the other hand, up-regulation of miR-375 and miR-21-5p are observed in SCLC cells of pulmonary neuroendocrine tumors of the lung [95, 96]. Again, miR-27a, miR-212, and miR-132 expressions were higher in solid tumors of lung adenocarcinoma whereas, miR-30d was shown to be up-regulated in mucinous invasive adenocarcinoma [97]. A higher expression of miR-182 was observed in primary lung tumors whereas miR-126 was highly expressed in metastatic lung tumors [98]. As miRNAs are readily found in the body fluids of humans, the detection of signature miRNA molecules could serve as a diagnostic tool for determining patients with high-risk of lung cancer.

Table 3 miRNAs, associated with the diagnosis and prognosis of lung cancer

miRNA/s	Found in	Expression	Reference/s
Diagnosis			
miR-205	Squamous cell carcinoma	Exclusively present	[92]
miR-124a	Adenocarcinoma	Exclusively present	[93]
miR-205, miR-93, miR-221, miR-30e	Squamous cell carcinoma	High	[94]
miR-29b, miR-29c, let-7e, miR-100, miR-125a-5p	Adenocarcinoma	High	[94]
miR-375, miR-21-5p	Pulmonary neuroendocrine tumor	High	[95, 96]
miR-27a, miR-212, miR-132	Solid tumors of lung adenocarcinoma	High	[97]
miR-30d	Mucinous invasive adenocarcinoma	High	[97]
miR-182	Primary lung tumor	High	[98]
miR-126	Metastatic lung tumor	High	[98]
Prognosis			
let-7	Lung adenocarcinoma	Low	[99]
miR-155, miR-21	Lung adenocarcinoma	High	[100]

miR microRNA

5.2 miRNAs in lung cancer prognosis

miRNAs often serve as a prognostic marker of lung cancer. For example, patients with surgical lung cancer often exhibit a lower expression of let 7 which is correlated with a shorter survival rate [99]. On the other hand, a higher expression of miR-155 and miR-21 has a negative impact on overall survival of patients, suffering from non-small cell lung adenocarcinoma [100].

6 miRNAs and therapeutic treatment of lung cancer

Therapeutic treatment of lung cancer includes chemotherapy, radiotherapy, molecular targeted therapy, and immunotherapy, in which miRNAs are shown to play an important role.

Table 4 miRNAs, contributing to the sensitivity and resistance in different lung cancer therapies

Therapy	miRNA	Up/down	Target/s	References
Chemotherapy	miR-539	Up	DCLK1	[116]
(Sensitive)	miR-9	Up	eIF5A2	[102]
	miR-106b-5p	Up	PKD2	[117]
	miR-202	Up	Ras/MAPK	[118]
	miR-140	Up	SIRT1/ROS/JNK	[119]
Chemotherapy	miR-324-5p	Up	FBXO11	[120]
(Resistant)	miR-130b	Up	PTEN	[121]
	miR-144-3p	Up	Nrf2	[122]
	miR-181b	Down	Bcl-2	[123]
	miR-133b	Down	GSTP1	[124]
	miR-221	Up	PTEN	[125]
Radiotherapy	miR-99a	Up	ATF2, mTOR	[126]
(Sensitive)	miR-200a	Up	HGF/c-Met	[127]
	miR-144-5p	Up	ATF2	[128]
	miR-18a-5p	Up	ATM and HIF1α	[129]
	miR-373	Up	TIMP2	[130]
Radiotherapy	miR-21	Up	HIF1α	[131]
(Resistant)	miR-1323	Down	PRKDC	[132]
	miR-198	Down	HGF/c-Met	[133]
Targeted therapy	miR-200c	Up	PI3K/AKT	[134]
(Sensitive)	miR-135a	Up	Rac1	[135]
Targeted therapy	miR-138	Down	HOXA4	[136]
(Resistant)	miR-181a	Up	GAS7	[137]
	miR-873	Up	GLI1	[138]
	miR-483-3p	Up	Integrin β3/FAK/ERK	[109]

miR microRNA, *DCLK1* doublecortin-like kinase protein 1, *eIF5A2* eukaryotic translation initiation factor 5A2, *PKD2* polycystin-2, *Ra* rat sarcoma, *MAPK* mitogen-activated protein kinase, *SIRT1* sirtuin (silent mating type information regulation 2 homolog) 1 (*S. cerevisiae*), *JNK* c-Jun N-terminal kinase, *FBXO11* F-box only protein 11, *PTEN* phosphatase and tensin homolog, *Nrf2* nuclear factor erythroid 2–related factor 2, *Bcl-2* B-cell leukemia/lymphoma 2 protein, *GSTP1* glutathione S-transferase pi 1, *ATF2* activating transcription factor-2, mammalian target of rapamycin, *HGF* hepatocyte growth factor, *c-Met* mesenchymal-epithelial transition factor, *HIF-1α* hypoxia inducible factor 1α, *ATM* Ataxia telangiectasia mutated, *TIMP2* tissue inhibitor of metalloproteinases 2, *PRKDC* protein kinase, DNA-activated, catalytic subunit, *PI3K* phosphoinositide 3-kinase, *Rac1* Ras-related C3 botulinum toxin substrate 1, *HOXA4* homeobox A4, *GAS7* growth arrest-specific protein 7, *GLI1* glioma-associated oncogene homolog, a zinc finger protein, *FAK* focal adhesion kinase, *ERK* extracellular regulated kinase

6.1 Chemotherapy

The chemotherapeutic regimen of lung cancer basically includes the treatment of platinum drugs, such as cisplatin and carboplatin, although NSCLC cells are found to be resistant against platinum-based drugs resulting in poorer efficacy of the treatment. miRNAs also contribute to the chemotherapy sensitivity and drug resistance of lung cancer. Cisplatin sensitivity in NSCLC cells is decreased significantly in miR-155 over-expressive conditions [101]. Another miRNA, miR-128-3p, which activates Wnt/β-Catenin and TGFβ pathways, is often found to be up-regulated in NSCLC cells, conferring resistance against chemotherapy [102]. In some instances, miR-96 is shown to impart resistance against cisplatin-induced apoptosis in NSCLC cells via the down-regulation of SAMD9 [103]. A brief information regarding other different miRNAs and their effect in a chemotherapy regimen in lung cancer is shown in Table 4.

6.2 Radiotherapy

Radiotherapy, the use of radioactive rays to destroy cancer cells, is often used successfully against NSCLC and SCLC. However, some cancer cells develop resistance against radiation, thereby resulting in a relapse of patients' post-radiotherapy. As radiotherapy often targets cell cycle, programmed cell death and DNA damage, it is indispensable to find out appropriate markers affecting radiotherapy resistance. miRNAs often play a vital role in this process. For example, miR-155 reduces the sensitivity of radiotherapy against lung cancer cells by targeting FOXO3A and TP53INP1 and miR-155 inhibition is shown to improve the sensitivity of radiotherapy [104]. Moreover, miR-18a down-regulation is associated with increased sensitivity of lung cancer cells to radiotherapy [105]. A list of miRNAs, involved in radiotherapy sensitivity or resistance against lung cancer is given in Table 4.

6.3 Molecular targeted therapy

miRNAs are often shown to be involved in various targeted therapies against lung cancer. Extracellular growth factor receptor (EGFR) signaling plays a crucial role in the growth and development of lung cancer by promoting tumor cell proliferation and angiogenesis, while inhibiting tumor apoptosis [106, 107]. EGFR, upon activation, induces intracellular tyrosine kinase (TK) phosphorylation which in turn, activates PI3K/AKT, JAK/STAT and Ras/Raf/MAPK pathways leading to tumor growth and survival. TK inhibitors (TKI), such as gefitinib and erlotinib are successfully used to treat lung cancer patients, sensitive to EGFR signaling [108]. miR-483-3p is shown to inhibit the metastatic potential of gefitinib-resistant lung cancer cells principally via the downregulation of EMT and miR-483-3p over-expression improves the sensitivity of these cells to gefitinib [109]. Other miRNAs, associated with targeted therapy against lung cancer, are listed in Table 4.

6.4 Immunotherapy

As mentioned before, PD-L1/PD-1 signaling plays an important part in the immune evasion mechanism of certain lung cancers [110, 111]. miR-140 directly targets PD-L1 in NSCLC cells thereby inhibiting PD-L1/Cyclin E pathway to restrict NSCLC cell proliferation [112] and thus, the miR-140/PD-L1/Cyclin E pathway could be used as a potential therapeutic target against NSCLC.

6.5 miRNA Mimics and anti-miRNAs as targeted therapeutics

miRNA Mimics can be used as a replacement of the down-regulated miRNAs by over-expressing with a miRNA-expressing vector, whereas knockdown of specific up-regulated miRNAs can be carried out with the help of antisense miRNAs (anti-miRNAs). miR-34a Mimics, entrapped in a liposome, MRX34 was already introduced in a phase I clinical trials and shown to exhibit anti-tumor activities [113]. Another miRNA, miR-16, packaged into a nano-cell, termed as TargomiR was enrolled to evaluate the optimum dose to treat patients with advanced NSCLC [114]. On the other hand, miR-421 knock down by Anti-miRNA, antisense morpholino (AMO) improves paclitaxel sensitivity to NSCLC cells both in vitro and in vivo [115].

7 miRNAs as lung cancer biomarkers

A biomarker can be defined as any measurable biological substance which indicates either normal or abnormal pathophysiological condition or any pharmacological responses against therapy [139]. In numerous occasions, miRNAs have been considered as potential diagnostic, prognostic, and therapeutic biomarkers in the context of lung cancer. For example, the expression of miR-492 and miR-590-3p is shown to be significantly up-regulated while miR-631 expression is down-regulated in the serum of NSCLC patients as compared to healthy individuals, therefore these three signature miRNAs are considered as potential biomarkers for early detection of NSCLC [140]. Moreover, as compared to healthy controls, the expression of miR-130a, miR-25, and miR-191* is found to be well-elevated in the sera of NSCLC patients. Both in vitro lung cancer cell model system and in vivo studies on murine system indicates that the expression of these three signature miRNA molecules gets further up-regulated upon radiation exposure [140]. Therefore, these signature miRNAs can be used as potential biomarkers for NSCLC progression [140]. Similarly, a study by Jiang et al. has demonstrated that four signature miRNAs, miR-210, miR-1290, miR-150, and miR-21-5p are over-expressed in the plasma of NSCLC patients with respect to benign lung disease or healthy controls which is negatively correlated with disease-free

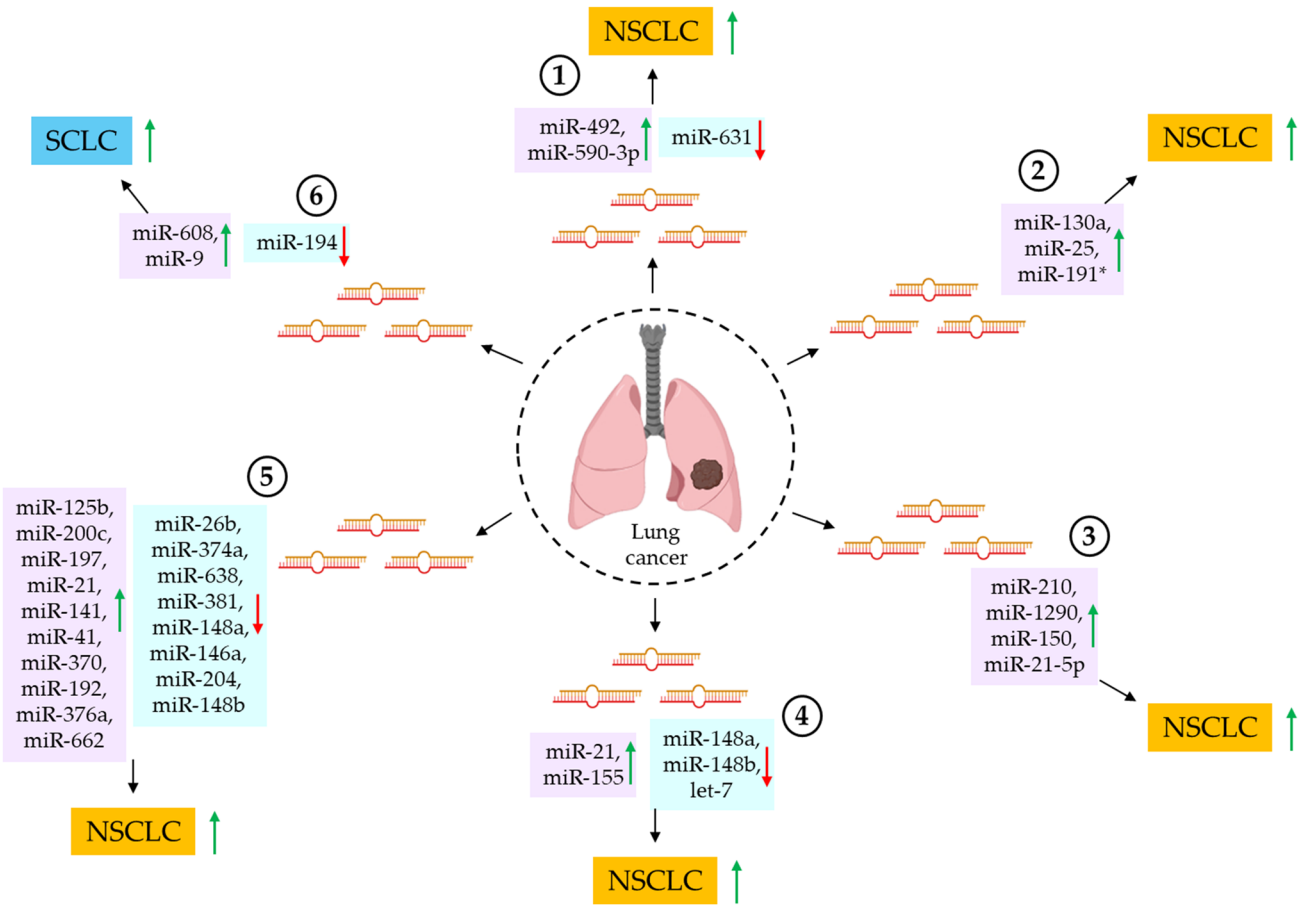

Fig. 4 miRNAs as predictive biomarkers for lung cancer. 1. The expression of miR-492 and miR-590-3p is up-regulated while miR-631 expression is down-regulated in the sera of NSCLC patients which is associated with NSCLC progression. 2. An up-regulation of miR-130a, miR-25, and miR-191* expression in the sera of NSCLC patients positively correlates with the disease progression. 3. miR-210, miR-1290, miR-150, and miR-21-5p expression in the plasma of NSCLC patients is shown to be associated with NSCLC progression. 4. Moreover, miR-21 and miR-155 expressions are elevated while the expressions of miR-148a, miR-148b, and let-7 is shown to be down-regulated in NSCLC patients which shows positive correlation with NSCLC progression. 5. Ten signature miRNAs (miR-125b, miR-200c, miR-197, miR-21, miR-141, miR-41, miR-370, miR-192, miR-376a, and miR-662) are up-regulated while eight signature miRNAs (miR-26b, miR-374a, miR-638, miR-381, miR-148a, miR-146a, miR-204, and miR-148b) are down-regulated in NSCLC, contributing to NSCLC pathogenesis. 6. An elevated expression of miR-608 and miR-9 while a down-regulation of miR-194 expression is shown to be associated with SCLC progression. The green upwards arrows indicate up-regulation or promotion; red downwards arrows indicate down-regulation. *NSCLC* non-small cell lung cancer, *SCLC* small cell lung cancer, *miR* microRNA

Table 5 miRNA-associated ongoing lung cancer clinical trials (based on clinical trial database 'https://clinicaltrials.gov/' accessed on 20th July 2024

Lung cancer type	Trial name	NCT number	Characteristics	Study type
All	Improving the Early Detection of Lung Cancer by Combining Exosomal Analysis of Hypoxia With Standard of Care Imaging (LungExoDETECT)	NCT04629079	Duration: Oct 2020–Oct 2024 Population: 800 Sex: M & F Age: ≥ 18y	Observational
All	Lung Cancer Prevention Screening Programme in Italy (RISP)	NCT05766046	Duration: Sep 2022–Sep 2026 Population: 7324 Sex: M & F Age: 55–75y	Interventional
SCC	Serum Exosomal miRNA Predicting the Therapeutic Efficiency in Lung Squamous Carcinoma	NCT05854030	Duration: April 2022–Aug 2023 Population: 60 Sex: M & F Age: ≥ 18y	Observational
NSCLC	Sotorasib in Advanced KRASG12C mutated Non-small Cell Lung Cancer Patients With Comorbidities (SOLUCOM)	- NCT05311709	Duration: May 2022–March 2025 Population: 100 Sex: M & F Age: ≥ 18y	Interventional (phase II)
NSCLC	Image-Guided, Intensity-Modulated Photon or Proton Beam Radiation Therapy in Treating Patients With Stage II-IIIB Non-small Cell Lung cancer	NCT01629498	Duration: Sep 2012–Sep 2025 Population: 100 Sex: M & F Age: ≥ 18y	Interventional (phase I & II)
NSCLC	Concomitant Radiotherapy, Tremelimumab & Durvalumab for Advanced NSCLC Patients Progressing on First-line Immunotherapy (CORAL-Lung)	NCT05000710	Duration: Dec 2021–Dec 2026 Population: 29 Sex: M & F Age: child, adult, older adult	Interventional (phase II)
All	Supplementation of n-3 PUFA in the Modulation of Lean Mass in Patients With Lung Cancer Receiving a High-protein Diet	NCT04965129	Duration: Nov 2022–March 2025 Population: 50 Sex: M & F Age: 20–90y	Interventional
All	OncoSweep Cancer Spotlight and Spectrum Product Line	NCT06261294	Duration: May 2023–March 2026 Population: 800 Sex: M & F Age: 18y	Observational
NSCLC	LIquid Biopsies in Patients Presenting Non-small Cell Lung Cancer (LIBIL)	NCT02511288	Duration: July 2015–Dec 2026 Population: 900 Sex: M & F Age: 18y	Observational
All	Limonene for Pulmonary Nodule Chemoprevention	NCT05525260	Duration: Feb 2023–Dec 2025 Population: 160 Sex: F Age: 45–75y	Interventional (phase I)

Table 5 (continued)

Lung cancer type	Trial name	NCT number	Characteristics	Study type
NSCLC	Papaverine in Combination With Chemoradiation for the Treatment of Stage II-III Non-small Cell Lung Cancer	NCT05136846	Duration: Dec 2021–Dec 2025 Population: 28 Sex: M & F Age: 18y	Interventional (phase I)
All	Leucoselect Phytosome for Neoadjuvant Treatment of Early Stage Lung Cancer	NCT04515004	Duration: Sep 2023–April 2027 Population: 30 Sex: M & F Age: 21y	Interventional (phase II)
NSCLC	A Machine Learning Approach to Identify Patients With Resected Non-small-cell Lung Cancer With High Risk of Relapse (MIRACLE)	NCT05732974	Duration: Mar 2023–Oct 2026 Population: 60 Sex: M & F Age: 18y	Observational

NCT national clinical trials, *M* male, *F* female, *y* years, *NSCLC* non-small cell lung cancer, *SCC* squamous cell carcinoma

survival of patients [141]. Thus, these four miRNAs act as promising biomarkers for early diagnosis and prognosis of NSCLC [141]. Previous studies have clearly demonstrated that increased expression of miR-21 and miR-155 and down-regulation of miR-148a, miR-148b and let-7 expression are associated with poor prognosis in NSCLC patients, hence making them potential candidates for NSCLC biomarkers [142]. Moreover, the expression of miR-26b, miR-374a, miR-638, miR-381, miR-148a, miR-146a, miR-204, and miR-148b are shown to be consistently down-regulated and miR-125b, miR-200c, miR-197, miR-21, miR-141, miR-41, miR-370, miR-192, miR-376a, and miR-662 are up-regulated in NSCLC, contributing to the poorer survival of the patients [143]. On the other hand, a higher expression of miR-194 is shown to be associated with longer SCLC overall survival whereas, a higher miR-608 and miR-9 expression profile in the sera of patient with SCLC can predict shorter overall patients survival [144]. Hence, miR-194, miR-608, and miR-9 expression profile can be used as a prognostic biomarker for SCLC [144]. Figure 4 briefly summarizes how altered expression of different miRNAs can be used as a predictive biomarker for different types of lung cancer.

8 miRNAs in lung cancer clinical trials

On several occasions, it has been found that the data obtained in preclinical studies often fails to be replicated while applied to humans. A drug showing promising results under in vitro and in vivo conditions often becomes ineffective or shows severe side effects on human subjects. Therefore, clinical trials on humans become necessary to check the effectiveness of a given drug before releasing into the market. Basically, a clinical trial consists of four phases. In phase I, the toxicity, optimum dose, and side effects of the given drug are analyzed upon application in a small group of patients (n = 15–20) [145]. In phase II also, the optimum dose, safety measurement, and efficacy of the drug are analyzed on a moderate number of patients (n = 100–300) [146, 147]. Clinical trial phase III involves a large number of patients (n = thousands) which again determines the efficacy and safety issues of the drug, based on which the drug is released into the market [148, 149]. The post-marketing analysis of the drug is performed in phase IV of clinical trials [150]. Different miRNAs are shown to be involved in the progression of lung cancer by various mechanisms and a fair number of clinical trials are ongoing which involves miRNAs associated with lung cancer. Table 5 briefly summarizes the miRNA-associated lung cancer clinical trials.

9 Conclusion and future directions

Lung cancer is considered as one of the leading causes of cancer-related death worldwide. The primary obstacles in the treatment of lung cancer include insufficient methods for early detection of lung cancer and the acquired drug resistance. The emergence of miRNA as one of the major contributors in the development and progression of lung cancer makes them a potential therapeutic target. The dysregulation of different miRNAs not only promotes lung cancer progression, but also confers drug resistance. However, the major pitfall of these miRNA-based therapeutics lies in the unique property of the miRNA, i.e., targeting more than one molecule which often leads to several off-target effects. The lack of appropriate delivery methods coupled with the off-target effects on the human system restrict its advancement from the laboratory to the clinics. Deeper and better knowledge is required for understanding their off-target effects. Moreover, population-based studies on a large scale are needed to recognize the therapeutic, diagnostic, and prognostic potential of the miRNAs in the progression of lung cancer. Another difficulty appears to be the contradictory results among different groups, which may be due to different approaches in sample collection, different specimens, sample storage conditions and analysis. A tremendous effort is required for the accuracy and reproducibility of the data to obtain a standard protocol and facilitating the use of miRNA-based therapeutics in clinics.

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Declarations

Ethics approval and consent to participate Not applicable.

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References

1. Siegel RL, et al. Cancer statistics, 2023. CA Cancer J Clin. 2023;73(1):17–48.
2. Gyoba J, et al. Diagnosing lung cancers through examination of micro-RNA biomarkers in blood, plasma, serum and sputum: a review and summary of current literature. Int J Mol Sci. 2016;17(4):494.
3. Morgensztern D, et al. Trends in stage distribution for patients with non-small cell lung cancer: a National Cancer Database survey. J Thorac Oncol. 2010;5(1):29–33.
4. Kanodra NM, Silvestri GA, Tanner NT. Screening and early detection efforts in lung cancer. Cancer. 2015;121(9):1347–56.
5. Das K, Rao LVM. The role of microRNAs in inflammation. Int J Mol Sci. 2022. https://doi.org/10.3390/ijms232415479.
6. Das K, et al. Factor VIIa suppresses inflammation and barrier disruption through the release of EEVs and transfer of microRNA 10a. Blood. 2022;139(1):118–33.
7. Das K, et al. Triple-negative breast cancer-derived microvesicles transfer microRNA221 to the recipient cells and thereby promote epithelial-to-mesenchymal transition. J Biol Chem. 2019;294(37):13681–96.
8. Parashar D, et al. MicroRNAs in extracellular vesicles: a potential role in cancer progression. Cell Signal. 2024;121: 111263.
9. Das K, et al. MicroRNA-10a enrichment in factor VIIa-released endothelial extracellular vesicles: potential mechanisms. J Thromb Haemost. 2024;22(2):441–54.
10. Kanwal M, Ding XJ, Cao Y. Familial risk for lung cancer. Oncol Lett. 2017;13(2):535–42.
11. Borges HL, Linden R, Wang JY. DNA damage-induced cell death: lessons from the central nervous system. Cell Res. 2008;18(1):17–26.
12. Jancík S, et al. Clinical relevance of KRAS in human cancers. J Biomed Biotechnol. 2010;2010: 150960.
13. Metro G, Crinò L. Advances on EGFR mutation for lung cancer. Transl Lung Cancer Res. 2012;1(1):5–13.
14. Rivlin N, et al. Mutations in the p53 tumor suppressor gene: important milestones at the various steps of tumorigenesis. Genes Cancer. 2011;2(4):466–74.
15. Huang C, et al. Upregulation and activation of p53 by erastin-induced reactive oxygen species contribute to cytotoxic and cytostatic effects in A549 lung cancer cells. Oncol Rep. 2018;40(4):2363–70.
16. Gu RH, et al. Diagnostic value of the combined detection of CEA, NSE and IL-18 for lung cancer and their relationship with apoptosis gene Bcl-2. J Biol Regul Homeost Agents. 2020;34(5):1637–46.
17. Li S, et al. Oridonin enhances the radiosensitivity of lung cancer cells by upregulating Bax and downregulating Bcl-2. Exp Ther Med. 2018;16(6):4859–64.
18. Yu F, et al. Combined effects of lung disease history, environmental exposures, and family history of lung cancer to susceptibility of lung cancer in Chinese non-smokers. Respir Res. 2021;22(1):210.
19. Baratella E, et al. Accuracy of CT-guided core-needle biopsy in diagnosis of thoracic lesions suspicious for primitive malignancy of the lung: a five-year retrospective analysis. Tomography. 2022;8(6):2828–38.
20. Baratella E, et al. Aging-related findings of the respiratory system in chest imaging: pearls and pitfalls. Curr Radiol Rep. 2023;11(1):1–11.
21. Jang HJ, et al. Relationship of the lung microbiome with PD-L1 expression and immunotherapy response in lung cancer. Respir Res. 2021;22(1):322.
22. Hiraku Y, et al. MicroRNA expression in lung tissues of asbestos-exposed mice: upregulation of miR-21 and downregulation of tumor suppressor genes Pdcd4 and Reck. J Occup Health. 2021;63(1): e12282.
23. Zhu K, et al. Tumor-suppressive miR-218-5p inhibits cancer cell proliferation and migration via EGFR in non-small cell lung cancer. Oncotarget. 2016;7(19):28075–85.
24. Qin Q, et al. miR-134 inhibits non-small cell lung cancer growth by targeting the epidermal growth factor receptor. J Cell Mol Med. 2016;20(10):1974–83.
25. Zhang G, et al. MicroRNA-338-3p suppresses cell proliferation and induces apoptosis of non-small-cell lung cancer by targeting sphingosine kinase 2. Cancer Cell Int. 2017;17:46.
26. He T, et al. MicroRNA-3613-5p promotes lung adenocarcinoma cell proliferation through a RELA and AKT/MAPK positive feedback loop. Mol Ther Nucleic Acids. 2020;22:572–83.
27. Tang J, et al. miR-21-5p/SMAD7 axis promotes the progress of lung cancer. Thorac Cancer. 2021;12(17):2307–13.

28. Zhang TX, et al. Clinical significance of miR-9-5p in NSCLC and its relationship with smoking. Front Oncol. 2024;14:1376502.
29. Xiao T, et al. NF-κB-regulation of miR-155, via SOCS1/STAT3, is involved in the PM(2.5)-accelerated cell cycle and proliferation of human bronchial epithelial cells. Toxicol Appl Pharmacol. 2019;377: 114616.
30. Bandi N, et al. miR-15a and miR-16 are implicated in cell cycle regulation in a Rb-dependent manner and are frequently deleted or down-regulated in non-small cell lung cancer. Cancer Res. 2009;69(13):5553–9.
31. Ren XS, et al. Tumor-suppressive microRNA-449a induces growth arrest and senescence by targeting E2F3 in human lung cancer cells. Cancer Lett. 2014;344(2):195–203.
32. Kong Q, et al. miR-641 functions as a tumor suppressor by targeting MDM2 in human lung cancer. Oncol Res. 2018;26(5):735–41.
33. Kumar MS, et al. Suppression of non-small cell lung tumor development by the let-7 microRNA family. Proc Natl Acad Sci U S A. 2008;105(10):3903–8.
34. Zhou Z, et al. Inhibition of the growth of non-small cell lung cancer by miRNA-1271. Am J Transl Res. 2015;7(10):1917–24.
35. Zheng Y-K, et al. MiR-122-5p regulates the mevalonate pathway by targeting p53 in non-small cell lung cancer. Cell Death Dis. 2023;14(4):234.
36. Das K, et al. Matrix metalloproteinase-2: a key regulator in coagulation proteases mediated human breast cancer progression through autocrine signaling. Biomed Pharmacother. 2018;105:395–406.
37. Kalluri R, Weinberg RA. The basics of epithelial-mesenchymal transition. J Clin Invest. 2009;119(6):1420–8.
38. Das K, Rao LVM. Coagulation protease-induced extracellular vesicles: their potential effects on coagulation and inflammation. J Thromb Haemost. 2024;22(11):2976–90.
39. Chen L, et al. Metastasis is regulated via microRNA-200/ZEB1 axis control of tumour cell PD-L1 expression and intratumoral immunosuppression. Nat Commun. 2014;5:5241.
40. Chen Y, et al. Decreased miRNA-148a is associated with lymph node metastasis and poor clinical outcomes and functions as a suppressor of tumor metastasis in non-small cell lung cancer. Oncol Rep. 2013;30(4):1832–40.
41. Wang H, et al. MicroRNA-29b attenuates non-small cell lung cancer metastasis by targeting matrix metalloproteinase 2 and PTEN. J Exp Clin Cancer Res. 2015;34(1):59.
42. Lin CW, et al. MicroRNA-135b promotes lung cancer metastasis by regulating multiple targets in the Hippo pathway and LZTS1. Nat Commun. 2013;4:1877.
43. Liu Z-L, et al. MicroRNA-21 (miR-21) expression promotes growth, metastasis, and chemo- or radioresistance in non-small cell lung cancer cells by targeting PTEN. Mol Cell Biochem. 2013;372(1):35–45.
44. Wu X, et al. miR-194 suppresses metastasis of non-small cell lung cancer through regulating expression of BMP1 and p27(kip1). Oncogene. 2014;33(12):1506–14.
45. Zvereva MI, Shcherbakova DM, Dontsova OA. Telomerase: structure, functions, and activity regulation. Biochemistry (Mosc). 2010;75(13):1563–83.
46. Choi JH, et al. TSA-induced DNMT1 down-regulation represses hTERT expression via recruiting CTCF into demethylated core promoter region of hTERT in HCT116. Biochem Biophys Res Commun. 2010;391(1):449–54.
47. Fabbri M, et al. MicroRNA-29 family reverts aberrant methylation in lung cancer by targeting DNA methyltransferases 3A and 3B. Proc Natl Acad Sci U S A. 2007;104(40):15805–10.
48. Choi YC, et al. Regulation of vascular endothelial growth factor signaling by miR-200b. Mol Cells. 2011;32(1):77–82.
49. Liu B, et al. MiR-126 restoration down-regulate VEGF and inhibit the growth of lung cancer cell lines in vitro and in vivo. Lung Cancer. 2009;66(2):169–75.
50. Hu J, et al. microRNA-128 plays a critical role in human non-small cell lung cancer tumourigenesis, angiogenesis and lymphangiogenesis by directly targeting vascular endothelial growth factor-C. Eur J Cancer. 2014;50(13):2336–50.
51. Mao G, et al. Tumor-derived microRNA-494 promotes angiogenesis in non-small cell lung cancer. Angiogenesis. 2015;18(3):373–82.
52. Das K, et al. Factor VIIa treatment increases circulating extracellular vesicles in hemophilia patients: implications for the therapeutic hemostatic effect of FVIIa. J Thromb Haemost. 2022;20(8):1928–33.
53. Das K, et al. Factor VIIa induces extracellular vesicles from the endothelium: a potential mechanism for its hemostatic effect. Blood. 2021;137(24):3428–42.
54. Das K, et al. The protease activated receptor2 promotes Rab5a mediated generation of pro-metastatic microvesicles. Sci Rep. 2018;8(1):7357.
55. Das K, et al. Protease-activated receptor 2 promotes actomyosin dependent transforming microvesicles generation from human breast cancer. Mol Carcinog. 2018;57(12):1707–22.
56. Das K, et al. A potential mechanism for the cytoprotective effects of activated protein C-released endothelial extracellular vesicles. Blood. 2024;143(16):1670–5.
57. Das K, et al. Factor VIIa releases phosphatidylserine-enriched extracellular vesicles from endothelial cells by activating acid sphingomyelinase. J Thromb Haemost. 2023;21(12):3414–31.
58. Das K et al. Extracellular vesicles in triple-negative breast cancer: immune regulation, biomarkers, and immunotherapeutic potential. Cancers (Basel). 2023; 15(19).
59. Das K et al. Beyond macromolecules: extracellular vesicles as regulators of inflammatory diseases. Cells. 2023; 12(15).
60. Das K, Mukherjee T, Shankar P. The role of extracellular vesicles in the pathogenesis of hematological malignancies: interaction with tumor microenvironment; a potential biomarker and targeted therapy. Biomolecules. 2023; 13(6).
61. Chatterjee M, et al. Circulating extracellular vesicles: an effective biomarker for cancer progression. Front Biosci (Landmark Ed). 2024;29(11):375.
62. Chatterjee M, et al. The role of extracellular vesicles in the pathogenesis of gynecological cancer. Front Oncol. 2024;14:1477610.
63. Hsu YL, et al. Hypoxic lung cancer-secreted exosomal miR-23a increased angiogenesis and vascular permeability by targeting prolyl hydroxylase and tight junction protein ZO-1. Oncogene. 2017;36(34):4929–42.
64. Wang W, et al. Tumor-derived exosomal miRNA-141 promote angiogenesis and malignant progression of lung cancer by targeting growth arrest-specific homeobox gene (GAX). Bioengineered. 2021;12(1):821–31.

65. Kim DH, et al. Tumor-derived exosomal miR-619–5p promotes tumor angiogenesis and metastasis through the inhibition of RCAN1.4. Cancer Lett. 2020;475:2–13.
66. Wang YF, et al. MicroRNA-608 promotes apoptosis in non-small cell lung cancer cells treated with doxorubicin through the inhibition of TFAP4. Front Genet. 2019;10:809.
67. Elkady MA, et al. MicroRNA-567 inhibits cell proliferation and induces cell apoptosis in A549 NSCLC cells by regulating cyclin-dependent kinase 8. Saudi J Biol Sci. 2021;28(4):2581–90.
68. Xu C, et al. MiRNA-1469 promotes lung cancer cells apoptosis through targeting STAT5a. Am J Cancer Res. 2015;5(3):1180–9.
69. Li J, et al. miRNA-1284 inhibits cell growth and induces apoptosis of lung cancer cells. Mol Med Rep. 2017;16(3):3049–54.
70. Yang T, et al. MicroRNA-15a induces cell apoptosis and inhibits metastasis by targeting BCL2L2 in non-small cell lung cancer. Tumor Biol. 2015;36(6):4357–65.
71. Xiong S, et al. MicroRNA-7 inhibits the growth of human non-small cell lung cancer A549 cells through targeting BCL-2. Int J Biol Sci. 2011;7(6):805–14.
72. Liu M, et al. Downregulating microRNA-144 mediates a metabolic shift in lung cancer cells by regulating GLUT1 expression. Oncol Lett. 2016;11(6):3772–6.
73. Xu Y, et al. miRNA-199a-5p/SLC2A1 axis regulates glucose metabolism in non-small cell lung cancer. J Cancer. 2022;13(7):2352–61.
74. Zhai S, et al. Downregulation of miR-33b promotes non-small cell lung cancer cell growth through reprogramming glucose metabolism miR-33b regulates non-small cell lung cancer cell growth. J Cell Biochem. 2019;120(4):6651–60.
75. Zhao X, et al. MicroRNA-124 suppresses proliferation and glycolysis in non–small cell lung cancer cells by targeting AKT–GLUT1/HKII. Tumor Biol. 2017;39(5):1010428317706215.
76. Zhu B, et al. MicroRNA-31-5p enhances the Warburg effect via targeting FIH. FASEB J. 2019;33(1):545–56.
77. Juneja VR, et al. PD-L1 on tumor cells is sufficient for immune evasion in immunogenic tumors and inhibits CD8 T cell cytotoxicity. J Exp Med. 2017;214(4):895–904.
78. Cortez MA, et al. PDL1 Regulation by p53 via miR-34. J Natl Cancer Inst. 2016. https://doi.org/10.1093/jnci/djv303.
79. Fujita Y, et al. The clinical relevance of the miR-197/CKS1B/STAT3-mediated PD-L1 network in chemoresistant non-small-cell lung cancer. Mol Therapy. 2015;23(4):717–27.
80. Song N, et al. MicroRNA-138–5p suppresses non-small cell lung cancer cells by targeting PD-L1/PD-1 to regulate tumor microenvironment. Front Cell Dev Biol. 2020. https://doi.org/10.3389/fcell.2020.00540.
81. Liu W, et al. MicroRNA-4458 regulates PD-L1 expression to enhance anti-tumor immunity in NSCLC via targeting STAT3. Mol Biotechnol. 2021;63(12):1268–79.
82. Yin Y, et al. Tumor-secreted miR-214 induces regulatory T cells: a major link between immune evasion and tumor growth. Cell Res. 2014;24(10):1164–80.
83. Greten FR, Grivennikov SI. Inflammation and cancer: triggers, mechanisms, and consequences. Immunity. 2019;51(1):27–41.
84. Virga F et al. MicroRNA-mediated metabolic shaping of the tumor microenvironment. Cancers (Basel). 2021; 13(1).
85. Kuninty PR, et al. MicroRNA targeting to modulate tumor microenvironment. Front Oncol. 2016;6:3.
86. Zhang J, et al. miR-101 represses lung cancer by inhibiting interaction of fibroblasts and cancer cells by down-regulating CXCL12. Biomed Pharmacother. 2015;74:215–21.
87. Li J, et al. mir-1-Mediated paracrine effect of cancer-associated fibroblasts on lung cancer cell proliferation and chemoresistance. Oncol Rep. 2016;35(6):3523–31.
88. Fortunato O, et al. Circulating mir-320a promotes immunosuppressive macrophages M2 phenotype associated with lung cancer risk. Int J Cancer. 2019;144(11):2746–61.
89. Lin L, et al. miR-130a regulates macrophage polarization and is associated with non-small cell lung cancer. Oncol Rep. 2015;34(6):3088–96.
90. Ke Y, et al. miR-149 inhibits non-small-cell lung cancer cells EMT by targeting FOXM1. Biochem Res Int. 2013;2013: 506731.
91. Yang L, et al. MircoRNA-33a inhibits epithelial-to-mesenchymal transition and metastasis and could be a prognostic marker in non-small cell lung cancer. Sci Rep. 2015;5:13677.
92. Lebanony D, et al. Diagnostic assay based on hsa-miR-205 expression distinguishes squamous from nonsquamous non-small-cell lung carcinoma. J Clin Oncol. 2009;27(12):2030–7.
93. Lujambio A, et al. Genetic unmasking of an epigenetically silenced microRNA in human cancer cells. Cancer Res. 2007;67(4):1424–9.
94. Zhang YK, et al. miRNAs expression profiling to distinguish lung squamous-cell carcinoma from adenocarcinoma subtypes. J Cancer Res Clin Oncol. 2012;138(10):1641–50.
95. Nishikawa E, et al. miR-375 is activated by ASH1 and inhibits YAP1 in a lineage-dependent manner in lung cancer. Cancer Res. 2011;71(19):6165–73.
96. Demes M, et al. Differential miRNA-expression as an adjunctive diagnostic tool in neuroendocrine tumors of the lung. Cancers (Basel). 2016. https://doi.org/10.3390/cancers8040038.
97. Nadal E, et al. A microRNA cluster at 14q32 drives aggressive lung adenocarcinoma. Clin Cancer Res. 2014;20(12):3107–17.
98. Barshack I, et al. MicroRNA expression differentiates between primary lung tumors and metastases to the lung. Pathol Res Pract. 2010;206(8):578–84.
99. Takamizawa J, et al. Reduced expression of the let-7 microRNAs in human lung cancers in association with shortened postoperative survival. Cancer Res. 2004;64(11):3753–6.
100. Yang M, et al. High expression of miR-21 and miR-155 predicts recurrence and unfavourable survival in non-small cell lung cancer. Eur J Cancer. 2013;49(3):604–15.
101. Lu J, et al. MicroRNAs associated with therapy of non-small cell lung cancer. Int J Biol Sci. 2018;14(4):390–7.
102. Cai J, et al. Simultaneous overactivation of Wnt/beta-catenin and TGFbeta signalling by miR-128-3p confers chemoresistance-associated metastasis in NSCLC. Nat Commun. 2017;8:15870.
103. Wu L, et al. miR-96 induces cisplatin chemoresistance in non-small cell lung cancer cells by downregulating SAMD9. Oncol Lett. 2016;11(2):945–52.
104. Babar IA, et al. Inhibition of hypoxia-induced miR-155 radiosensitizes hypoxic lung cancer cells. Cancer Biol Ther. 2011;12(10):908–14.

105. Shen Z, et al. Effect of miR-18a overexpression on the radiosensitivity of non-small cell lung cancer. Int J Clin Exp Pathol. 2015;8(1):643–8.
106. Cox G, et al. Prognostic significance of platelet and microvessel counts in operable non-small cell lung cancer. Lung Cancer. 2000;29(3):169–77.
107. Giatromanolaki A, et al. Prognostic value of angiogenesis in operable non-small cell lung cancer. J Pathol. 1996;179(1):80–8.
108. Solassol I, Pinguet F, Quantin X. FDA- and EMA-approved tyrosine kinase inhibitors in advanced EGFR-mutated non-small cell lung cancer: safety, tolerability, plasma concentration monitoring, and management. Biomolecules. 2019; 9(11).
109. Yue J, et al. Epigenetic silencing of miR-483-3p promotes acquired gefitinib resistance and EMT in EGFR-mutant NSCLC by targeting integrin beta3. Oncogene. 2018;37(31):4300–12.
110. Paul S, Mukherjee T, Das K. Coagulation protease-driven cancer immune evasion: potential targets for cancer immunotherapy. Cancers (Basel). 2024; 16(8).
111. Paul S, et al. Coagulation factor VIIa enhances programmed death-ligand 1 expression and its stability in breast cancer cells to promote breast cancer immune evasion. J Thromb Haemost. 2023;21(12):3522–38.
112. Xie WB, et al. MiR-140 expression regulates cell proliferation and targets PD-L1 in NSCLC. Cell Physiol Biochem. 2018;46(2):654–63.
113. Beg MS, et al. Phase I study of MRX34, a liposomal miR-34a mimic, administered twice weekly in patients with advanced solid tumors. Invest New Drugs. 2017;35(2):180–8.
114. van Zandwijk N, et al. Safety and activity of microRNA-loaded minicells in patients with recurrent malignant pleural mesothelioma: a first-in-man, phase 1, open-label, dose-escalation study. Lancet Oncol. 2017;18(10):1386–96.
115. Duan FG, et al. MicroRNA-421 confers paclitaxel resistance by binding to the KEAP1 3'UTR and predicts poor survival in non-small cell lung cancer. Cell Death Dis. 2019;10(11):821.
116. Deng H, et al. miR-539 enhances chemosensitivity to cisplatin in non-small cell lung cancer by targeting DCLK1. Biomed Pharmacother. 2018;106:1072–81.
117. Yu S, et al. MicroRNA-106b-5p regulates cisplatin chemosensitivity by targeting polycystic kidney disease-2 in non-small-cell lung cancer. Anticancer Drugs. 2017;28(8):852–60.
118. Sun W, et al. miR-202 enhances the anti-tumor effect of cisplatin on non-small cell lung cancer by targeting the Ras/MAPK pathway. Cell Physiol Biochem. 2018;51(5):2160–71.
119. Lin Z, et al. MiR-140 resensitizes cisplatin-resistant NSCLC cells to cisplatin treatment through the SIRT1/ROS/JNK pathway. Onco Targets Therapy. 2020;13:8149–60.
120. Ba Z, et al. miR-324-5p upregulation potentiates resistance to cisplatin by targeting FBXO11 signalling in non-small cell lung cancer cells. J Biochem. 2019;166(6):517–27.
121. Zhang Q, et al. MicroRNA-130b targets PTEN to induce resistance to cisplatin in lung cancer cells by activating Wnt/beta-catenin pathway. Cell Biochem Funct. 2018;36(4):194–202.
122. Yin Y, et al. miR-144-3p regulates the resistance of lung cancer to cisplatin by targeting Nrf2. Oncol Rep. 2018;40(6):3479–88.
123. Liu HN, et al. miR-181b inhibits chemoresistance in cisplatin-resistant H446 small cell lung cancer cells by targeting Bcl-2. Arch Med Sci. 2018;14(4):745–51.
124. Lin C, et al. miR-133b reverses cisplatin resistance by targeting GSTP1 in cisplatin-resistant lung cancer cells. Int J Mol Med. 2018;41(4):2050–8.
125. Wang N, et al. Negative regulation of PTEN by microRNA-221 and its association with drug resistance and cellular senescence in lung cancer cells. Biomed Res Int. 2018;2018:7908950.
126. Yin H, et al. MiR-99a enhances the radiation sensitivity of non-small cell lung cancer by targeting mTOR. Cell Physiol Biochem. 2018;46(2):471–81.
127. Du M, et al. MicroRNA-200a suppresses migration and invasion and enhances the radiosensitivity of NSCLC cells by inhibiting the HGF/c-Met signaling pathway. Oncol Rep. 2019;41(3):1497–508.
128. Song L, et al. miR-144-5p enhances the radiosensitivity of non-small-cell lung cancer cells via targeting ATF2. Biomed Res Int. 2018;2018:5109497.
129. Chen X, et al. Radiosensitizing effects of miR-18a-5p on lung cancer stem-like cells via downregulating both ATM and HIF-1alpha. Cancer Med. 2018;7(8):3834–47.
130. Guo Y, et al. RETRACTED: down-regulation of miR-373 increases the radiosensitivity of lung cancer cells by targeting TIMP2. Int J Biochem Cell Biol. 2018;99:203–10.
131. Jiang S, et al. MicroRNA-21 modulates radiation resistance through upregulation of hypoxia-inducible factor-1alpha-promoted glycolysis in non-small cell lung cancer cells. Mol Med Rep. 2016;13(5):4101–7.
132. Li Y, et al. Knockdown of microRNA-1323 restores sensitivity to radiation by suppression of PRKDC activity in radiation-resistant lung cancer cells. Oncol Rep. 2015;33(6):2821–8.
133. Zhu L, et al. MicroRNA-198 inhibition of HGF/c-MET signaling pathway overcomes resistance to radiotherapy and induces apoptosis in human non-small-cell lung cancer. J Cell Biochem. 2018;119(9):7873–86.
134. Zhou G, et al. miR-200c enhances sensitivity of drug-resistant non-small cell lung cancer to gefitinib by suppression of PI3K/Akt signaling pathway and inhibites cell migration via targeting ZEB1. Biomed Pharmacother. 2017;85:113–9.
135. Zhang T, Wang N. miR-135a confers resistance to gefitinib in non-small cell lung cancer cells by upregulation of RAC1. Oncol Res. 2018;26(8):1191–200.
136. Tang X, et al. HOXA4-regulated miR-138 suppresses proliferation and gefitinib resistance in non-small cell lung cancer. Mol Genet Genomics. 2019;294(1):85–93.
137. Ping W, et al. MiR-181a contributes gefitinib resistance in non-small cell lung cancer cells by targeting GAS7. Biochem Biophys Res Commun. 2018;495(4):2482–9.
138. Jin S, et al. MiR-873 inhibition enhances gefitinib resistance in non-small cell lung cancer cells by targeting glioma-associated oncogene homolog 1. Thorac Cancer. 2018;9(10):1262–70.
139. Ahmad A, Imran M, Ahsan H. Biomarkers as biomedical bioindicators: approaches and techniques for the detection, analysis, and validation of novel biomarkers of diseases. Pharmaceutics. 2023;15(6):1630.

140. Duan X, et al. Circulating miRNAs in serum as biomarkers for early diagnosis of non-small cell lung cancer. Front Genet. 2021;12: 673926.
141. Jiang H-G, et al. Four plasma miRNAs act as biomarkers for diagnosis and prognosis of non-small cell lung cancer. Oncol Lett. 2021;22(5):792.
142. Lamichhane SR, et al. Prognostic role of microRNAs in human non-small-cell lung cancer: a systematic review and meta-analysis. Dis Markers. 2018;2018:8309015.
143. Xiao W, et al. Prognostic value of microRNAs in lung cancer: a systematic review and meta-analysis. Mol Clin Oncol. 2019;10(1):67–77.
144. Yan H, et al. A three microRNA-based prognostic signature for small cell lung cancer overall survival. J Cell Biochem. 2019;120(5):8723–30.
145. Ivy SP, et al. Approaches to phase 1 clinical trial design focused on safety, efficiency, and selected patient populations: a report from the clinical trial design task force of the national cancer institute investigational drug steering committee. Clin Cancer Res. 2010;16(6):1726–36.
146. Stallard N. Optimal sample sizes for phase II clinical trials and pilot studies. Stat Med. 2012;31(11–12):1031–42.
147. Estey EH, Thall PF. New designs for phase 2 clinical trials. Blood. 2003;102(2):442–8.
148. Mahajan R, Gupta K. Adaptive design clinical trials: methodology, challenges and prospect. Indian J Pharmacol. 2010;42(4):201–7.
149. Lowenstein PR, Castro MG. Uncertainty in the translation of preclinical experiments to clinical trials. Why do most phase III clinical trials fail? Curr Gene Ther. 2009;9(5):368–74.
150. Zhang X, et al. Overview of phase IV clinical trials for postmarket drug safety surveillance: a status report from the ClinicalTrials.gov registry. BMJ Open. 2016;6(11): e010643.