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# The microRNA-34 Family and Its Functional Role in Lung Cancer

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**Abstract:** Lung cancer is one of the most common malignant tumors in humans and the leading cause of cancer-related deaths worldwide. The microRNA-34 (miR-34) family is dysregulated in various human cancers and is an important family of tumor suppressor genes among microRNAs. The miR-34 family is downregulated in lung cancer. It inhibits cell proliferation, metastasis, and invasion, arrests the cell cycle, and induces apoptosis or senescence by negatively regulating many oncogenes. It is commonly used to detect and treat lung cancer. This study describes the regulatory role of the miR-34 family in lung cancer and the associated research advances in treatment.

**Key Words:** Lung cancer, miR-34a, miR-34b, miR-34c

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With an estimated 2 million new cases and 1.76 million deaths each year, lung cancer is one of the most common malignancies in humans.[1] Lung cancer can be divided into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Small cell lung cancer accounts for ~15% of all diagnosed lung cancers, and non-small cell lung cancer accounts for ~85% of all lung cancers. Non-small cell lung cancer is divided into adenocarcinoma (ADC), squamous cell carcinoma (SCC), and large cell carcinoma (LCC). Despite some advances in the detection and treatment of lung cancer in recent years, it remains the leading cause of cancer-related deaths worldwide.

MicroRNAs (miRNAs, miRs) are a class of short, non-coding RNAs that can affect most cellular processes, such as cell metabolism, proliferation, differentiation, and apoptosis, and can act as oncogenes or tumor suppressor genes in human malignancies.[2] The study revealed that miRNAs, such as miR-21, miR-146-5p, miR-17-5p, miR-210, miR-17-92, miR-135a-5p, miR-484, miR-186-5p, and miR-1246 can act as oncogenes in lung cancer progression and can be used as tumor suppressor genes include the let-7 family, miR-29 family, miR-34 family, miR-200 family, miR-513-3p, miR-382, miR-19a-3p, miR-99b-5p, miR-590-5p, miR-320a, miR-106-5p, and miR-186, which are promising biomarkers and novel therapeutic targets in lung cancer.[3]

The miR-34 family is known to be dysregulated in various human cancers, including colorectal cancer, prostate cancer, breast cancer, liver cancer, osteosarcoma, and lung cancer.[4] The miR-34 family is considered a tumor suppressor miRNA because of its synergy with the well-known tumor suppressor gene *p53*.[4–6] *p53* is a crucial tumor suppressor gene, which undergoes mutations in over half of human cancers.[7] Mutations in the *p53* pathway are one of the important occurrences in lung cancer. The positive feedback regulatory network formed by *p53* and the miR-34 family can suppress the growth and metastasis of tumor cells.[7] The miR-34 family plays an important tumor suppressor role as a downstream target of *p53* (Fig. 1), which blocks tumor progression, arrests cell cycle, and induces apoptosis or senescence by negatively regulating a series of target genes.[8] The miR-34 family was the first miRNA directly regulated by the tumor suppressor gene *p53*. The miR-34 family plays an important role in the diagnosis, treatment, drug resistance, and prognosis of various cancers, including lung cancer. The miR-34 family is downregulated in lung cancer, exerting anticancer effects by regulating biological processes such as proliferation, migration, invasion, and apoptosis of NSCLC cells.[9] In conclusion, the miR-34 family plays a key role in lung cancer, and its involvement in various aspects of lung cancer biology makes it a promising candidate for further research.

The miR-34 family includes 3 members (miR-34a, miR-34b, and miR-34c). Three members are located at 2 separate chromosomal loci.[10] MiR-34a is encoded in the second exon of a gene located on chromosome 1p36.22, whereas miR-34b and miR-34c share a common host gene located on chromosome 11q23.1.[5] The mature sequences of the 3 members differed slightly (Fig. 2).

Two mature miRNAs have been identified for each member of the miR-34 family (miR-34a-5p, miR-34a-3p, miR-34b-5p, miR-34b-3p, miR-34c-5p, miR-34c-3p).[11]

The maturation of the miRNA chain is a complex process. The formation of the 5p chain is accomplished by the cleavage of microprocessor complexes (Drosha and DGCR8), and the 3p chain is formed by Dicer cleavage.[11] The 5p members of the miR-34 family are involved in cell proliferation, apoptosis, migration, and invasion, but the role of the 3p chain and its targets is largely unknown.[11]

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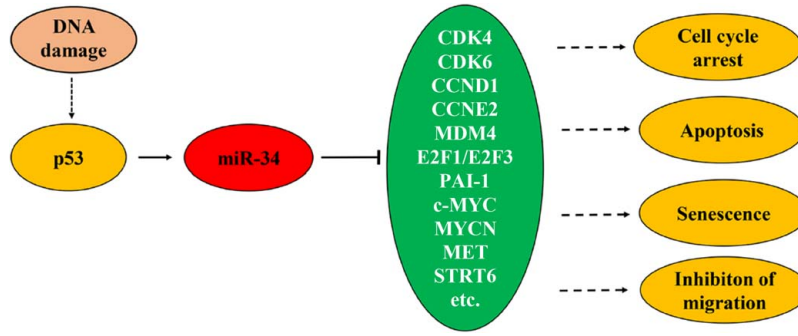


**FIGURE 1.** The miR-34 family plays an important tumor suppressor role by *p53*. The miR-34 family members are direct *p53* targets, and their ectopic expression can inhibit migration, arrest cell cycle, and induce apoptosis and senescence. full color online

The regulatory role of the miR-34 family in lung cancer and the latest research advancements in treatment were elucidated in this study. The potential clinical significance of this molecule in the realm of lung cancer was examined, offering novel insights for clinical approaches to the prevention and treatment of the disease.

## THE REGULATORY ROLE OF THE miR-34 FAMILY IN LUNG CANCER

### The Regulatory Role of miR-34a in Lung Cancer

MiR-34a is the best-studied tumor suppressor miRNA.[2] MiR-34a was found to be significantly down-regulated in NSCLC tissues and cell lines.[12] MiR-34a can inhibit tumor growth by targeting *CCNE1*,[13] *EGFR*,[12] and *SIRT6*,[14] inhibit the growth of CD44hi strain-like NSCLC cells,[15] and inhibit growth and metastasis by increasing the expression of *PTEN* and *YY1*, but the expression of *CDK6* decreases in lung cancer.[16] *p53* enhances the transcription of miR-34a, and overexpression of miR-34a inhibits proliferation, arrests the cell cycle, and induces senescence in lung cancer cells by targeting *E2F1*/*E2F3*.[17] In the *lncRNA FEZF1-AS1*/miR-34a/*NOTCH1* network, overexpression of miR-34a can target *NOTCH1* to play an important role as a tumor suppressor.[18] MiR-34a can inhibit proliferation and promote apoptosis by inhibiting the target genes *PDGFR-α*,[19] *TGFβR2*,[20] and *AXL*[21] while reducing the migratory and invasive abilities of NSCLC.[19] The expression of miR-34a is negatively correlated with the expression of *c-MET* and *CDK6* in NSCLC and has prognostic importance for recurrence-free survival (RFS) in patients with lung adenocarcinoma.[22] Tissue and plasma miR-34a expression was negatively correlated with lymph node metastasis, and high plasma miR-34a expression was associated with prolonged disease-free survival (DFS) and overall survival (OS).[23] The mature sequence of miR-34a, miR-34a-5p, is under-expressed in lung adenocarcinoma cells and exerts anticancer effects by targeting *HMMR*.[24] MiR-34a-5p also plays a key role in luteolin (LTL)-induced anti-tumor effects by targeting *MDM4* and enhancing activation of the *p53* signaling pathway, inhibiting tumor growth and inducing apoptosis in NSCLC cells.[25] High expression of miR-34a-5p enhances *p21* expression and promotes cellular senescence in NSCLC.[26] The epithelial-mesenchymal transition (EMT) contributes to cancer progression and is widely recognized as a key process required for cancer metastasis.[3] Studies have shown that miR-34a can directly target *PAI-1* to block its expression and inhibit the EMT process to suppress NSCLC metastasis.[27] However, it has also been shown that miR-34a can induce EMT in *p53* wild-type NSCLC, which can lead to further progression of cancer.[28]

### The Regulatory Role of miR-34b in Lung Cancer

The expression of miR-34b was significantly down-regulated in the tissues of patients with NSCLC compared with the adjacent tissues.[9,29,30] In patients with SCC, miR-34b/c decreased earlier and more significantly than miR-34a, and the effect of miR-34b/c was greater than that of miR-34a.[9] The expression level of miR-34b was negatively correlated with lymph node metastasis and pathologic stage and positively correlated with the degree of differentiation.[29] Lower miR-34b expression was associated with higher distant lymph node metastasis.[31] The expression of miR-34b and *p53* in NSCLC tissues is positively correlated, and

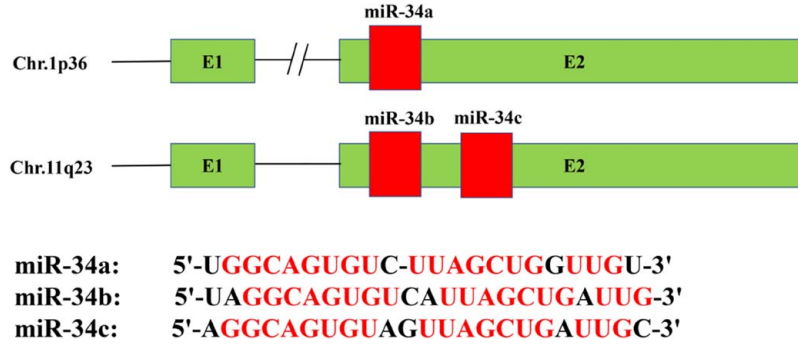


**FIGURE 2.** Alignment of structure and mature sequence of genomic loci of miR-34 family members. The red nucleotides in the mature sequence are the same in miR-34a, miR-34b, and miR-34c. full color online

the high expression of miR-34b and *p53* is closely related to the clinical stage and pathologic grade of NSCLC.[29] MiR-34b and *p53* can be important tumor markers for non-small cell lung cancer. *MET* and miR-34b serve as key nodes in the *p53* network, miR-34b downregulates *MET*, and *p53* conversely upregulates miR-34b in a feedback loop, thereby inhibiting cell proliferation by inducing apoptosis.[30] MiR-34b can inhibit the migration and invasion of NSCLC cells and promotes their apoptosis by targeting *YAF2*.[32] Contrary to the expression of miR-34a/c, the study found that the frequency of miR-34b was significantly increased in the serum of NSCLC patients.[33] The expression level of miR-34b-3p in the plasma of NSCLC patients was significantly higher than that of the pulmonary tuberculosis group and the healthy control group and correlated with the tumor diameter, which could be an independent risk factor for the occurrence of NSCLC.[34] MiR-34b-3p is downregulated in both NSCLC tumor tissues and lung cancer cell lines (H1299 and A549), which may exert a tumor suppressor effect by targeting *CDK4*.[35] MiR-34b-3p can also inhibit proliferation and induce apoptosis of A549 and H1299 cells by targeting *TGFBR1*.[36] The study found that expression of miR-34b-3p was downregulated in clinical SCLC tissue samples and its ectopic high expression also significantly inhibited cancer cell invasiveness.[37] Both miR-34b/c inhibit EMT, and miR-34b/c may be a more potent tumor suppressor than miR-34a.[10]

## The Regulatory Role of miR-34c in Lung Cancer

Compared with normal controls, miR-34c is downregulated in lung cancer and may act as a potential tumor suppressor gene.[19,38,39] Low expression of miR-34c is associated with the formation of distant metastases in lung adenocarcinoma.[31] MiR-34c acts as a tumor suppressor by targeting *HMGB1* to induce stress in the endoplasmic reticulum.[40] MiR-34c can inhibit cell proliferation and induce apoptosis while reducing the migratory and invasive abilities of NSCLC cells by targeting *PDGFR-β*[19] and *IL-6*.[38] The expression of miR-34c-3p was significantly reduced in tissues, serum, and cell lines from NSCLC patients.[41,42] MiR-34c-3p inhibits the proliferation and invasion of NSCLC by targeting *eIF4E*[41] and *PAC1*/*MAPK* signaling pathways.[42] In patients with *KRAS*-mutated NSCLC, high expression of miR-34c-3p is associated with longer survival and acts as a targeted modulator of the *CDK1* gene, providing tailored therapy.[43] MiR-34c-5p plays an important tumor suppressor role in both the *lncRNA POU6F2-AS1*/miR-34c-5p/*KCNJ4* network[44] and the *circPTCH1*/miR-34c-5p/*MYCN* network,[45] which can become a new therapeutic strategy. High expression of miR-34c in plasma predicts longer DFS.[23] Analysis of exosomes from clinical serum samples revealed that miR-34c-3p expression was significantly downregulated in exosomes from NSCLC patients compared with normal controls, and exosomes with low levels of miR-34c-3p were able to accelerate NSCLC invasion and migration by targeting integrin *α2β1*.[46]

Therefore, the miR-34 family is an important tumor suppressor gene in lung cancer. They can inhibit tumor cell proliferation, cloning, EMT, migration, invasion, arrest the cell cycle, and promote apoptosis by negatively regulating many downstream target genes (Table 1, Fig. 3).

## miR-34 FAMILY AND THE TREATMENT OF LUNG CANCER

The current standard of treatment for lung cancer is surgery, combined with radiation and chemotherapy, as well as targeted therapy and immunotherapy, however, most lung cancer patients are always diagnosed at an advanced stage for various reasons and lose the opportunity for surgery. Hence, nonsurgical treatment has become a primary treatment for advanced lung cancer. However, radioresistance and chemoresistance have become the main obstacles to the successful treatment of lung cancer patients, and the miR-34 family could play an active role in lung cancer treatment.

### miR-34 Family and Radiotherapy

It has been reported that miR-34a overexpression can increase the radiosensitivity of NSCLC cells by targeting *LyGDI*, which can be used as a radiosensitizer in NSCLC treatment.[47] MiR-34a inhibits double-strand break repair in NSCLC cells and increases radiosensitivity through the regulation of *RAD51*.[48] MiR-34a can promote ionizing radiation (IR)-induced senescence of tumor cells by targeting *Myc*, which could be a new therapeutic strategy to improve the efficacy of radiotherapy in lung cancer.[49] Overexpression of miR-34b also increased radiosensitivity under low-dose radiation in *p53* wild-type, *KRAS*-mutated NSCLC cells.[50]

### miR-34 Family and Chemotherapy

Cisplatin (CDDP) is the most effective and widely used chemotherapy drug for the treatment of lung cancer, but the failure of CDDP chemotherapy is a common phenomenon in lung cancer. Owing to the high mortality and morbidity caused by lung cancer, it is important to improve the efficacy of CDDP chemotherapy.[51] Apoptotic inhibition, EMT, and cancer stem cell (CSC) progression are several key factors in chemoresistance, and restoring the dysregulated miR-34 family through various approaches contributes to resensitization to chemoresistance.[8]

High expression levels of miR-34a are associated with shorter OS in patients, which could be a possible predictor of the effectiveness of palliative chemotherapy in SCC patients.[52] Compared with CDDP-insensitive NSCLC controls, CDDP-sensitive NSCLC patients had upregulated miR-34a expression, and *p53* could induce miR-34a expression and increased NSCLC sensitivity to CDDP by targeting *MYCN*.[53] In the *lncRNA SNHG14*/miR-34a/*HMGB1* network, miR-34a inhibited NSCLC progression and promoted the sensitivity of NSCLC cells to CDDP.[54] MiR-34a overexpression increases the sensitivity of A549 cells to CDDP-induced cytotoxicity by targeting *PEBP4*.[55] MiR-34a-5p inhibits tumor cell proliferation, migration, and invasion and reverses CDDP resistance by targeting *TRIM29* while inducing apoptosis in NSCLC cells.[56] MiR-34a-5p can also inhibit the growth of CDDP-resistant NSCLC cells by targeting *TNFAIP8*.[57] MiR-34c-3p expression was significantly reduced in tissue samples from chemotherapy-resistant and metastatic NSCLC patients, and overexpression of miR-34c-3p may target *NOTCH1* to sensitize NSCLC cells to paclitaxel and CDDP.[58]

However, conflicting studies have found that miR-34c-5p can protect lung cancer cells from paclitaxel-induced apoptosis by interfering with *p53* levels and targeting *c-Myc* levels, thereby increasing chemoresistance.[59] Similar studies also revealed that miR-34c-5p expression was significantly

**TABLE 1.** The Regulatory Role of the miR-34 Family in Lung Cancer

| MiR-34 Family Members | Upstream Regulatory Genes | Target Gene | Regulation | References |
|---|---|---|---|---|
| miR-34a | | *EGFR* | Inhibits proliferation and migration, arrests cell cycle, promotes apoptosis | 12 |
| miR-34a | | *CCNE1* | Inhibits proliferation and cloning | 13 |
| miR-34a | | *SIRT6* | Inhibits proliferation, arrests cell cycle, promotes apoptosis | 14 |
| miR-34a | | *CDK6* | Inhibits proliferation, migration, and invasion, promotes apoptosis | 16 |
| miR-34a | *p53* | *E2F1/E2F3* | Inhibits proliferation, arrests cell cycle, promotes aging | 17 |
| miR-34a | *lncRNA FEZF1-AS1* | *NOTCH1* | Inhibits migration and invasion | 18 |
| miR-34a | | *PDGFR-α* | Inhibits tumor growth, migration, invasion, and promotes apoptosis | 19 |
| miR-34a | | *TGFβR2* | Inhibits proliferation, promotes apoptosis | 20 |
| miR-34a | | *AXL* | Promotes apoptosis | 21 |
| miR-34a | | *c-MET, CDK6* | Prognosis of recurrence | 22 |
| miR-34a | | *PAI-1* | Suppresses EMT | 27 |
| miR-34a-5p | *HCG18* | *HMMR* | Inhibits proliferation, migration, and invasion, promotes apoptosis | 24 |
| miR-34a-5p | | *MDM4* | Inhibits tumor growth, promotes apoptosis | 25 |
| miR-34b | | *YAF2* | Inhibits migration and invasion, promotes apoptosis | 32 |
| miR-34b | | *MET* | Promotes apoptosis | 30 |
| miR-34b-3p | | *CDK4* | Inhibits proliferation, arrests cell cycle, promotes apoptosis | 35 |
| miR-34b-3p | | *TGFBR1* | Inhibits migration and invasion | 36 |
| miR-34c | | *PDGFR-β* | Inhibits tumor growth, migration, invasion, and promotes apoptosis | 19 |
| miR-34c | | *IL-6* | Inhibits proliferation, promotes apoptosis | 38 |
| miR-34c | | *HMGB1* | Inhibits proliferation, promotes apoptosis, induces stress in the endoplasmic reticulum | 40 |
| miR-34c-3p | | *eIF4E* | Inhibits proliferation, migration and invasion, arrests cell cycle | 41 |
| miR-34c-3p | | *PAC1* | Promotes apoptosis | 42 |
| miR-34c-3p | | *CDK1* | Inhibits proliferation, promotes apoptosis | 43 |
| miR-34c-5p | *lncRNA POU6F2-AS1* | *KCNJ4* | Inhibits proliferation, cloning, migration, and invasion | 44 |
| miR-34c-5p | *circPTCH1* | *MYCN* | Inhibits migration, invasion, and EMT | 45 |

increased in drug-resistant A549/DDP cells compared with that A549 cells, which could be related to the drug resistance-associated gene *RRAS*.[60]

Resistance to conventional chemotherapy remains a major challenge in cancer treatment. Chemoresistance leads to cancer relapse and poor prognosis. The miR-34 family has shown different prognostic roles in chemotherapy and may serve as a predictive factor for the effectiveness of chemotherapy in patients with lung cancer. However, the decision to choose a chemotherapy regimen based solely on the expression of the miR-34 family may not be common in clinical settings currently. The involvement of the miR-34 family in regulating various cellular processes suggests that evaluating the expression levels of the miR-34 family can

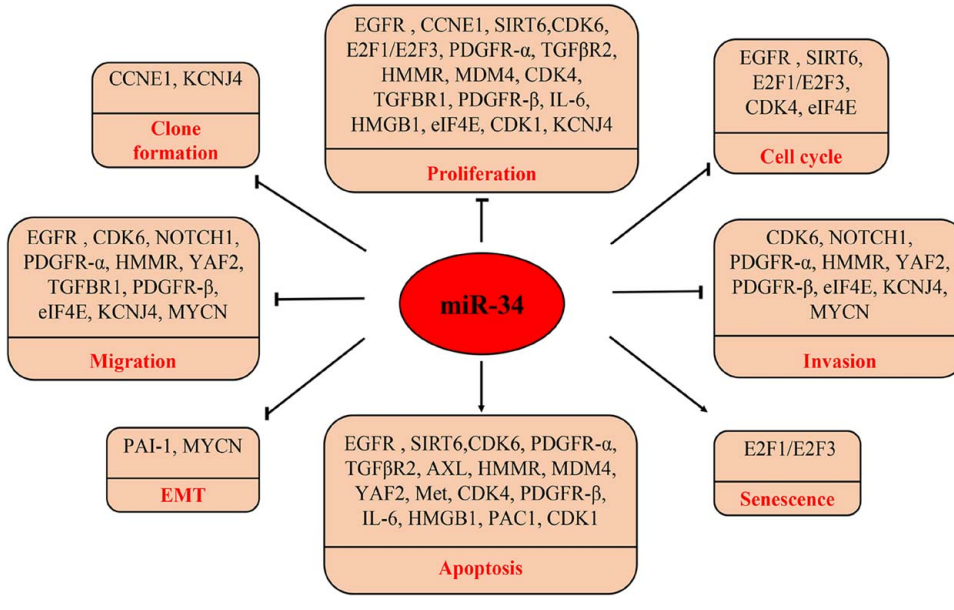


**FIGURE 3.** The regulatory role of the miR-34 family in lung cancer. full color online

provide additional information about tumor biology and potential responses to chemotherapy. However, when determining the most suitable chemotherapy approach for individual patients, various factors must be considered, including specific cancer types, staging, and other biomarkers. A multidisciplinary team consisting of oncologists, pathologists, and researchers must evaluate the available evidence and make informed decisions on treatment strategies. With the development of personalized medicine and biomarker-guided treatment strategies, integrating miR-34 family expression analysis into the decision-making process for selecting chemotherapy regimens may hold promise in the future.

## miR-34 Family and Targeted Therapy

In recent years, targeted therapy has emerged as a clinical alternative for the treatment of NSCLC. The epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) is widely used as targeted therapy in the treatment of NSCLC; however, it is effective in only some cases of NSCLC and remains resistant in most cases. Combination therapy is a promising strategy to overcome drug resistance; however, it is often hindered by the lack of suitable adjunctive therapies.[61] Because of its ability as a tumor suppressor, miRNA is an attractive adjunct therapy candidate for treating NSCLC.[61] Increasingly, studies indicate that altered miRNA expression is a key factor in the potential mechanisms of primary and acquired resistance to tyrosine kinase inhibitors (TKIs) in lung cancer.[62,63]

The combination of miR-34a and EGFR-TKI can synergistically increase the sensitivity of *EGFR* wild-type and mutant NSCLC cells to the drug, representing a strategy to overcome the primary and acquired resistance of NSCLC to EGFR-TKI.[64] These data suggest that there is a strong synergy between erlotinib and miR-34a mimics in therapy, and when combined with miR-34a, most NSCLC cells can be resensitized to erlotinib.[65] Combination therapy with miRNAs (let-7b and miR-34a) can effectively target multiple cellular pathways that affect cancer cell proliferation and erlotinib resistance, and NSCLC cells can be sensitized to erlotinib.[61] In a gefitinib resistance study, miR-34a was found to overcome hepatocyte growth factor (HGF)-mediated resistance to gefitinib in *EGFR*-mutated lung cancer cells by targeting *MET*.[66] *LncRNA MIAT* interacts with miR-34a and epigenetically controls miR-34a expression by hypermethylation of its promoter, thereby sensitizing lung cancer cells to gefitinib.[67] MiR-34a can play a resensitizing role in NSCLC-acquired gefitinib resistance by targeting AXL.[68] MiR-34a-5p and *lncRNA HOTAIR* interact to inhibit EMT, resulting in increased sensitivity to the berberine-gefitinib combination drug.[69]

In contrast, research has systematically and comprehensively examined the targeted therapy mechanism for cancer and discovered that in A549 and H1975 cell lines, resistance to osimertinib is associated with the upregulation of miR-34a-5p.[70] Combining the relevant literature indicates that miR-34a-5p may be positively correlated with osimertinib resistance in NSCLC.[70]

## miR-34 Family and Immunotherapy

Recently, immunotherapy has emerged as an important treatment option for NSCLC. Several studies have identified miR-34a as a therapeutic biomarker candidate for response to immune checkpoint inhibitor therapy, whereas miR-34b affects the expression of programmed cell death-ligand 1 (PD-L1) and programmed cell death-1 (PD-1).[71] *PD-L1* is a direct target of miR-34a confirmed by western blotting and luciferase assays, and *p53* regulates *PD-L1* via miR-34a to regulate tumor immune escape.[72] A study characterized a new *lncRNA OIP5-AS1*/miR-34a/*PD-L1* axis that is involved in the progression of NSCLC.[73] Overexpression of miR-34a reduced the expression level of *PD-L1*.[73] MiR-34a plays a key role in the expression of *PD-L1*, and Gallic Acid can inhibit *PD-L1* expression by upregulating miR-34a.[74] 6-Gingerol inhibits the expression of *PD-L1* by upregulating miR-34a, thereby exhibiting antiproliferative activity in NSCLC cells.[75] MiR-34a-5p and miR-34c-5p, as *PD-L1* inhibitory miRNAs, when ectopically expressed, suppress the development of NSCLC and can significantly regulate the cell cycle, migration, clonogenicity, invasion, cell apoptosis, tumor chemosensitivity, and host anti-tumor immune response.[76] In ADC, miR-34a is a negative regulatory factor of CD47-mediated anti-phagocytic cell activity.[77] MiR-34a mimics disrupt the *KRAS*/*CD47* signaling axis, inhibit *CD47* expression, enhance macrophage phagocytosis, and restore innate immune surveillance.[77] In NSCLC, the overexpression of miR-34a-5p in macrophages can inhibit *KLF4*, leading to the polarization of macrophages from the M2 phenotype to the M1 phenotype, thereby reducing tumor occurrence.[78]

In summary, the miR-34 family may be one of the pathways to enhance the effectiveness of lung cancer immunotherapy. Further research on the regulation of the miR-34 family and their combination with immunotherapy in terms of molecular mechanisms and clinical applications is necessary to improve the prognosis of patients in lung cancer treatment.

Therefore, the miR-34 family can improve the sensitivity to radiotherapy and chemotherapy by inhibiting target genes, overcoming resistance to targeted drugs, and evading immunotherapy (Table 2, Fig. 4). The miR-34 family is an important regulatory gene in lung cancer treatment and plays an important and beneficial role in lung cancer treatment.

## miR-34 Mimics Therapy

The miR-34 family is a tumor-suppressive miRNA. Downregulation of the miR-34 family is commonly observed in tumor cells. It plays a crucial role in regulating various cellular processes such as tumor cell proliferation, cell cycle progression, apoptosis, and senescence. By reintroducing synthetic miR-34 mimics into cancer cells, their tumor-suppressive functions can be restored. The multi-target action of miRNA can regulate the entire signaling network[2] and various cellular signaling pathways.[79] Supplementing downregulated miRNAs with synthetic oligonucleotides or suppressing over-expressed miRNAs with artificial antagonists has become a common strategy in cancer research.[2] This makes miRNAs are becoming increasingly attractive tools and suitable therapeutics for the development of cancer therapies.

With the application of the first mimic-based miRNA drug MRX34 in the Phase I clinical trial (NCT01829971), the importance of the miR-34 family is being increasingly recognized.[4] MRX34, a first-in-class cancer therapy developed by miRNA Therapeutics, shows strong activity in melanoma, hepatocellular carcinoma, NSCLC, and kidney cancer.[2] MRX34 is a liposome miR-34a analog, which initiated its first Phase I clinical trial in 2013. Unfortunately, in 2016, the trial was halted by the U.S. Food and Drug

**TABLE 2.** The Regulatory Role of the miR-34 Family in the Treatment of Lung Cancer

| MiR-34 Family Members | Upstream Regulatory Genes | Target Gene | Treattype | Regulation | Mechanism | References |
|---|---|---|---|---|---|---|
| miR-34a | | *LyGDI* | Radiotherapy | Increased radiosensitivity | Promotes apoptosis | 47 |
| miR-34a | | *RAD51* | Radiotherapy | Increased radiosensitivity | Inhibits double-strand break repair | 48 |
| miR-34a | | *c-Myc* | Radiotherapy | Increased radiosensitivity | Promotes aging | 49 |
| miR-34a | *p53* | *MYCN* | Chemotherapy | Increased cisplatin sensitivity | Inhibits growth, induces apoptosis | 53 |
| miR-34a | *lncRNA SNHG14* | *HMGB1* | Chemotherapy | Increased cisplatin sensitivity | Inhibits migration and invasion, promotes apoptosis | 54 |
| miR-34a | | *PEBP4* | Chemotherapy | Increased cisplatin sensitivity | Promotes apoptosis | 55 |
| miR-34a-5p | *lncRNA TP73-AS1* | *TRIM29* | Chemotherapy | Increased cisplatin sensitivity | Inhibits proliferation, migration, invasion, and promotes apoptosis | 56 |
| miR-34a-5p | *circHUWE1* | *TNFAIP8* | Chemotherapy | Increased cisplatin sensitivity | Inhibits proliferation, migration, and invasion, promotes apoptosis, arrests cell cycle | 57 |
| miR-34c-3p | | *NOTCH1* | Chemotherapy | Increased sensitivity to paclitaxel and cisplatin | Inhibits migration, promotes apoptosis | 58 |
| miR-34c-5p | | *c-Myc* | Chemotherapy | Increased paclitaxel resistance | Inhibits apoptosis | 59 |
| miR-34a | | *MET* | Targeted therapy | Overcame gefitinib resistance | Inhibits growth, induces apoptosis | 66 |
| miR-34a | *lncRNA MIAT* | | Targeted therapy | Overcame gefitinib resistance | Regulation of *PI3K*/*Akt* signaling pathway | 67 |
| miR-34a | | *AXL* | Targeted therapy | Overcame gefitinib resistance | Regulation of *PI3K*/*Akt*, *MEK*/*ERK*, and *JAK*/*STAT* signaling pathways | 68 |
| miR-34a-5p | *lncRNA HOTAIR* | | Targeted therapy | Improved efficacy of berberine and gefitinib combination | Suppresses EMT | 69 |
| miR-34a | *p53* | *PD-L1* | Immunotherapy | Improved efficacy | Inhibits immune escape | 72 |
| miR-34a | *lncRNA OIP5-AS1* | *PD-L1* | Immunotherapy | Improved efficacy | Inhibits immune escape | 73 |
| miR-34a | | *CD47* | Immunotherapy | Enhanced macrophage phagocytosis | Restores innate immune surveillance | 77 |
| miR-34a-5p | | *KLF4* | Immunotherapy | Reduced tumor occurrence | Leads to the polarization of macrophages | 78 |

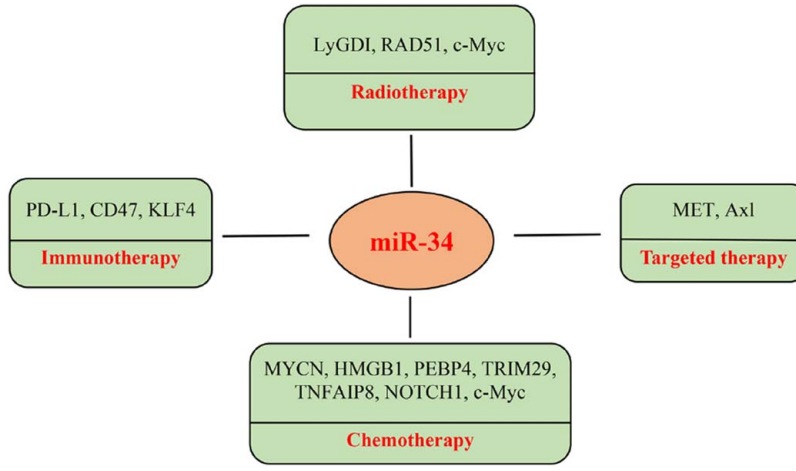


**FIGURE 4.** The regulatory role of the miR-34 family in the treatment of lung cancer. full color online

Administration (FDA) due to serious immune-mediated adverse events (AEs) that resulted in the deaths of 4 patients.[80,81] Nonetheless, this initial clinical trial of miRNA-based cancer therapy provided valuable insights for the future development of such drugs.

However, some challenges have emerged in the application of miR-34a therapy. One of them is the low efficiency of miRNA delivery to tumor cells.[5] The delivery system used in this clinical trial is liposome nanoparticles.[80] Although this liposome nanoparticle design achieved efficient absorption and long circulation time of miR-34a in the blood, it does not directly target the specific delivery of miR-34a to cancer cells. This nonspecific targeted delivery may be one of the potential reasons for the premature termination of the trial. Some studies have analyzed that the possible reason is that miRNA is degraded and RNase is abundant in serum, which easily denatures miR-34a, causing miR-34a to fail to penetrate the capillary endothelium and reach target cells.[4] Second, the immune response deserves attention. In 2016, the clinical trial of MRX34 (NCT02862145) was withdrawn due to the occurrence of 5 immune-related AEs.[4] In the latest report of the clinical trial of MRX34, severe AEs include sepsis, hypoxia, cytokine release syndrome, and liver failure, which suggest an immune-mediated toxicity pattern,[81] possibly involving lipid nanoparticle-associated double-stranded RNA (dsRNA)-related nonspecific inflammation and miR-34a-related gene expression-specific regulation. Unfortunately, the preclinical AE spectrum of MRX34 in animals, including nonhuman primates, cannot predict the immune activation spectrum in humans.[81] Third, this multi-targeting nature of miRNAs can lead to off-target side effects. Systemic overexpression of the miR-34 family, which is widespread and regulates physiological processes, can target genes in healthy tissues and cause side effects such as cardiovascular disease.[79] The fourth consideration is drug dosage. In the initial stages of this clinical trial, the dosage started at 10 mg/m$^2$ and then increased to 124 mg/m$^2$.[80] However, due to the observed systemic inflammatory response syndrome in patients, the 124 mg/m$^2$ dosage was determined to be higher than the maximum tolerated dose (MTD). Subsequently, the dosage was modified to 110 mg/m$^2$ and administered with dexamethasone in the first week, aimed at suppressing the immune response.[81] However, this revised dosing schedule still resulted in severe AEs, with no apparent increase in efficacy. This indicates that the safety window for miR-34a appears to be small, and due to treatment-induced immune reactions, high-dose administration of miR-34a may not be beneficial clinically. Therefore, careful evaluation and control of the dosage and administration regimen of miR-34a in patients is necessary. The fifth challenge is the cost of production and delivery of miR-34 mimics. The synthesis process of miR-34-based therapeutic methods and the demand for specialized delivery systems lead to high treatment costs. Optimizing and simplifying the manufacturing process helps reduce overall costs, making it more affordable for patients. The sixth challenge is having reliable biomarkers to predict the response to miR-34-based therapy, which is crucial. The discovery of biomarkers is essential for patient stratification, enabling the selection of individuals most likely to benefit from miR-34 mimics. This personalized treatment approach will optimize treatment outcomes and minimize potential side effects. The seventh is that the treatment of miR-34a relies on nanocarriers, and the toxicity of nanoparticles is also worth discussing.[4] The development of many nano-carrier-based platforms has enhanced the study of cell-specific controlled delivery and safety of miRNA-based therapies.[2] The ideal delivery system[82] for miR-34a therapy should achieve 3 main goals: (1) effective delivery with high cellular uptake and stability, (2) specific delivery to tumors, while avoiding or minimizing nonspecific delivery to other normal tissues, and (3) minimizing systemic immune responses and immune toxicity.

From the first human clinical trial of miR-34a, we have learned that the dose and administration of miR-34a are strictly limited by immune-related toxicity. Therefore, combining miR-34a with other treatment modalities should maximize therapeutic benefits while minimizing immune toxicity-associated adverse effects related to miR-34a dosage. In recent years, it has been suggested that one approach to improving efficacy and reducing toxicity is to rationally identify small molecule drug combinations that synergize with miR-34a. Through high-throughput screening of a large panel of small molecules with known biological activities, ouabain was identified as a candidate small molecule that synergizes with miR-34a to activate autophagy to kill lung cancer cells, but it needs to be more fully scaled up studies.[83]

MiR-34 mimics, in combination with other therapeutic agents, have garnered significant attention for their ability to enhance cancer treatment outcomes. By simultaneously targeting multiple pathways involved in tumor growth and progression, a combined therapeutic approach can generate synergistic effects and amplify overall treatment results. Research has highlighted the potential benefits of synergistic delivery methods, suggesting that combining miR-34 mimics with conventional chemotherapy, targeted therapy, or immunotherapy could potentially overcome drug resistance, improve patient response, and hold great promise for combination therapies targeting multiple pathways.[84] According to the above principles, research has provided 4 possible clinical scenarios for the treatment of miR-34 mimics.[82] The first scenario involves treating early primary tumors, especially in early-stage tumors, where low doses of miR-34 treatment can be used as adjunct therapy alongside standard treatments to address preexisting cancer cell heterogeneity. The second clinical scenario is untreated advanced and metastatic tumors. At this stage, the clinical application of miR-34 will involve combination approaches with standard therapies. The third clinical scenario is treating failed and drug-resistant tumors, where miR-34 replacement therapy will be used in combination with chemotherapy and/or targeted therapy to overcome treatment resistance. The final clinical scenario is the application of miR-34 in *p53* mutant tumors, considering miR-34 is a direct transcriptional target of *p53*. In *p53* mutant tumors, miR-34 could potentially become a primary therapeutic agent.

In conclusion, miR-34 mimics therapy shows promise in the advancement of novel cancer treatments. Through continued exploration of its clinical application, improvement of delivery techniques, and conduct of clinical trials, miR-34 mimics may emerge as a valuable therapeutic intervention for fighting cancer and enhancing patient outcomes. Furthermore, the investigation of combination therapies and elucidation of novel mechanisms of action will enhance our comprehension and success in the development of innovative cancer treatments utilizing miR-34. It is essential to thoroughly assess the advantages and disadvantages of this emerging miRNA therapy, refine strategies to mitigate side effects, and promote its future utilization.[79]

## SUMMARY AND OUTLOOK

The miR-34 family is an important tumor suppressor gene in lung cancer. They can inhibit proliferation, cloning, migration, invasion, EMT, arrest cell cycle, and promote apoptosis. The miR-34 family can also improve the sensitivity of radiotherapy and chemotherapy through various regulatory effects, overcome drug resistance of targeted drugs and escape immunotherapy, and play an important and positive role in various treatment methods for lung cancer. In terms of mimetic therapy, the miR-34 family could become a rational anticancer drug in the future.

Translating the findings of preclinical research into clinical applications is crucial for the successful implementation of lung cancer therapy strategies based on miR-34. This can facilitate the transition of research results from the laboratory to clinical practice.

*Predictive biomarkers*. The expression levels of members of the miR-34 family have been studied as potential predictive biomarkers for therapy response in lung cancer patients. They can evaluate the diagnostic and prognostic potential of the miR-34 family as biomarkers for lung cancer.

*Patient stratification*. Studying whether miR-34 expression levels can stratify lung cancer patients into different risk groups or predict response to specific treatments can be a tool for personalized medicine. Treatment strategies can be customized based on individual patient characteristics.

*Mechanisms of drug resistance*. Further research on the molecular pathways regulated by the miR-34 family in lung cancer cells can help identify the impact of the miR-34 family on key carcinogenic processes such as cell proliferation, apoptosis, and metastasis. Developing strategies to overcome drug resistance in lung cancer treatment is vital, and studying the role of miR-34 family dysregulation in mediating drug resistance mechanisms can provide valuable insights for alternative treatment methods.

*Therapeutic development*. Combining the miR-34 family with other therapeutic strategies may be a promising approach to enhance the effectiveness of lung cancer treatment. Further exploration of using miR-34 mimics as therapeutic agents for lung cancer treatment, developing excellent and safe treatment systems using miR-34 mimics or inhibitors to specifically target lung cancer cells.

*Clinical trials*. Conducting preclinical studies to evaluate the efficacy and safety of miR-34-based treatments in relevant animal models. Future efforts should focus on designing and conducting phase I, II, and III clinical trials to assess the effectiveness of miR-34 treatment in lung cancer patients. Analyzing data generated from clinical trials to evaluate the efficacy and safety of interventions based on miR-34.

By following these detailed clinical translation methods, researchers can advance the miR-34 family in the field of lung cancer from the laboratory to the bedside, potentially improving patient outcomes and paving the way for personalized treatment strategies in lung cancer management.

## CONCLUSIONS

The miR-34 family has broad application prospects in the detection and treatment of lung cancer. In addition, it is need to further investigate the regulatory role of the miR-34 family, which could provide new ideas for the prevention, diagnosis, monitoring, and treatment of lung cancer.

## REFERENCES

1. Thai AA, Solomon BJ, Sequist LV, et al. Lung cancer. *Lancet*. 2021;398:535–554.
2. Reda El Sayed S, Cristante J, Guyon L, et al. MicroRNA therapeutics in cancer: current advances and challenges. *Cancers*. 2021;13:2680.
3. Tang S, Li S, Liu T, et al. MicroRNAs: emerging oncogenic and tumor-suppressive regulators, biomarkers and therapeutic targets in lung cancer. *Cancer Lett*. 2021;502:71–83.
4. Zhang L, Liao Y, Tang L. MicroRNA-34 family: a potential tumor suppressor and therapeutic candidate in cancer. *J Exp Clin Cancer Res*. 2019;38:53.
5. Rokavec M, Li H, Jiang L, et al. The p53/miR-34 axis in development and disease. *J Mol Cell Biol*. 2014;6:214–230.
6. Hermeking H. The miR-34 family in cancer and apoptosis. *Cell Death Differ*. 2010;17:193–199.
7. Pan W, Chai B, Li L, et al. p53/MicroRNA-34 axis in cancer and beyond. *Heliyon*. 2023;9:e15155.
8. Naghizadeh S, Mohammadi A, Duijf PHG, et al. The role of miR-34 in cancer drug resistance. *J Cell Physiol*. 2020;235:6424–6440.
9. Sun D, Wu Y, Zhang S, et al. Distinct roles of miR-34 family members on suppression of lung squamous cell carcinoma. *Biomed Pharmacother*. 2021;142:111967.

 

10. Kim JS, Kim EJ, Lee S, et al. MiR-34a and miR-34b/c have distinct effects on the suppression of lung adenocarcinomas. *Exp Mol Med*. 2019;51:1–10.
11. Córdova-Rivas S, Fraire-Soto I, Mercado-Casas Torres A, et al. 5p and 3p strands of miR-34 family members have differential effects in cell proliferation, migration, and invasion in cervical cancer cells. *Int J Mol Sci*. 2019;20:545.
12. Li Y, Liu X, Zhang C, et al. MicroRNA-34a/EGFR axis plays pivotal roles in lung tumorigenesis. *Oncogenesis*. 2017; 6:e372.
13. Han Z, Zhang Y, Yang Q, et al. miR-497 and miR-34a retard lung cancer growth by co-inhibiting cyclin E1 (CCNE1). *Oncotarget*. 2015;6:13149–13163.
14. Ruan L, Chen J, Ruan L, et al. miR-34a inhibits tumorigenesis of NSCLC via targeting SIRT6. *Int J Clin Exp Pathol*. 2018;11: 1135–1145.
15. Shi Y, Liu C, Liu X, et al. The microRNA miR-34a inhibits non-small cell lung cancer (NSCLC) growth and the CD44hi stem-like NSCLC cells. *PLoS One*. 2014;9:e90022.
16. Chen Y, Hou C, Zhao L, et al. The association of microrna-34a with high incidence and metastasis of lung cancer in Gejiu and Xuanwei Yunnan. *Front Oncol*. 2021;11:619346.
17. Ren J, Ding L, Xu Q, et al. LF-MF inhibits iron metabolism and suppresses lung cancer through activation of P53-miR-34a-E2F1/E2F3 pathway. *Sci Rep*. 2017;7:749.
18. Huang S, Li C, Huang J, et al. LncRNA FEZF1-AS1 promotes non-small lung cancer cell migration and invasion through the up-regulation of NOTCH1 by serving as a sponge of miR-34a. *BMC Pulm Med*. 2020;20:110.
19. Garofalo M, Jeon YJ, Nuovo GJ, et al. MiR-34a/c-dependent PDGFR-alpha/beta downregulation inhibits tumorigenesis and enhances TRAIL-induced apoptosis in lung cancer.. *PLoS One*. 2013;8:e67581.
20. Ma Z, Hou P, Li Y, et al. MicroRNA-34a inhibits the proliferation and promotes the apoptosis of non-small cell lung cancer H1299 cell line by targeting TGFβR2. *Tumor Biol*. 2015; 36:2481–2490.
21. Cho C, Huang J, Shiah S, et al. Negative feedback regulation of AXL by miR-34a modulates apoptosis in lung cancer cells. *RNA*. 2016;22:303–315.
22. Hong JH, Roh KS, Suh S, et al. The expression of microRNA-34a is inversely correlated with c-MET and CDK6 and has a prognostic significance in lung adenocarcinoma patients. *Tumor Biol*. 2015;36:9327–9337.
23. Zhao K, Cheng J, Chen B, et al. Circulating microRNA-34 family low expression correlates with poor prognosis in patients with non-small cell lung cancer. *J Thorac Dis*. 2017;9: 3735–3746.
24. Li W, Pan T, Jiang W, et al. HCG18/miR-34a-5p/HMMR axis accelerates the progression of lung adenocarcinoma. *Biomed Pharmacother*. 2020;129:110217.
25. Jiang Z, Li M, Qin Y, et al. Luteolin inhibits tumorigenesis and induces apoptosis of non-small cell lung cancer cells via regulation of microRNA-34a-5p. *Int J Mol Sci*. 2018;19:447.
26. Gupta S, Silveira DA, Mombach JCM. ATM/miR-34a-5p axis regulates a p21-dependent senescence-apoptosis switch in non-small cell lung cancer: a Boolean model of G1/S checkpoint regulation. *Febs Lett*. 2020;594:227–239.
27. Lin X, Lin B, Chen X, et al. PAI-1/PIAS3/Stat3/miR-34a forms a positive feedback loop to promote EMT-mediated metastasis through Stat3 signaling in non-small cell lung cancer. *Biochem Bioph Res Co*. 2017;493:1464–1470.
28. Kawami M, Takenaka S, Akai M, et al. Characterization of miR-34a-induced epithelial–mesenchymal transition in non-small lung cancer cells focusing on p53. *Biomolecules*. 2021;11: 1853.
29. Yang S, Zhu H, Cheng Q. Correlative analysis of miR-34b and p53 with pathological characteristics of NSCLC. *Oncol Lett*. 2019;17:5558–5564.
30. Wang LG, Ni Y, Su BH, et al. MicroRNA-34b functions as a tumor suppressor and acts as a nodal point in the feedback loop with Met. *Int J Oncol*. 2013;42:957–962.
31. Daugaard I, Knudsen A, Kjeldsen TE, et al. The association between miR-34 dysregulation and distant metastases formation in lung adenocarcinoma. *Exp Mol Pathol*. 2017;102:484–491.
32. Zhuang X, Zhao L, Guo S, et al. miR-34b inhibits the migration/invasion and promotes apoptosis of non-small-cell lung cancer cells by YAF2. *Eur Rev Med Pharmaco*. 2019;23: 2038–2046.
33. Halvorsen AR, Bjaanæs M, LeBlanc M, et al. A unique set of 6 circulating microRNAs for early detection of non-small cell lung cancer. *Oncotarget*. 2016;7:37250–37259.
34. Song Z, Zhang Z, Liu Y. The clinical application of plasma miR-34b-3p and miR-302a-5p in the diagnosis of non-small cell lung cancer. *Chinese Journal of Lung Cancer*. 2019;22: 216–222.
35. Feng H, Ge F, Du L, et al. miR-34b-3p represses cell proliferation, cell cycle progression and cell apoptosis in non-small-cell lung cancer (NSCLC) by targeting CDK4. *J Cell Mol Med*. 2019;23:5282–5291.
36. Lu X, Xu C, Xu Z, et al. Piperlongumine inhibits the growth of non-small cell lung cancer cells via the miR-34b-3p/TGFBR1 pathway. *BMC Complement Med Ther*. 2021;21:15.
37. Mizuno K, Mataki H, Arai T, et al. The microRNA expression signature of small cell lung cancer: tumor suppressors of miR-27a-5p and miR-34b-3p and their targeted oncogenes. *J Hum Genet*. 2017;62:671–678.
38. Jiang X, Li M, Ke L. miR-34c regulates the proliferation and apoptosis of lung cancer cells. *Clin Invest Med*. 2020;43: E56–E62.
39. Pak MG, Lee C, Lee W, et al. Unique microRNAs in lung adenocarcinoma groups according to major TKI sensitive EGFR mutation status. *Diagn Pathol*. 2015;10:99.
40. Tu L, Long X, Song W, et al. miR-34c acts as a tumor suppressor in non-small cell lung cancer by inducing endoplasmic reticulum stress through targeting HMGB1. *Onco Targets Ther*. 2019;12:5729–5739.
41. Liu F, Wang X, Li J, et al. miR-34c-3p functions as a tumour suppressor by inhibiting eIF4E expression in non-small cell lung cancer. *Cell Proliferat*. 2015;48:582–592.
42. Zhou YL, Xu YJ, Qiao CW. miR-34c-3p suppresses the proliferation and invasion of non-small cell lung cancer (NSCLC) by inhibiting PAC1/MAPK pathway. *Int J Clin Exp Pathol*. 2015;8:6312–6322.
43. Palma F, Affinito A, Nuzzo S, et al. miR-34c-3p targets CDK1 a synthetic lethality partner of KRAS in non-small cell lung cancer. *Cancer Gene Ther*. 2021;28:413–426.
44. Wu X, Xie Y, Zhou L, et al. Long noncoding RNA POU6F2-AS1 regulates lung cancer aggressiveness through sponging miR-34c-5p to modulate KCNJ4 expression. *Genet Mol Biol*. 2021;44:e20200050.
45. Shen Z, Sun S. CircPTCH1 promotes migration in lung cancer by regulating MYCN expression through miR-34c-5p. *Onco Targets Ther*. 2021;14:4779–4789.
46. Huang W, Yan Y, Liu Y, et al. Exosomes with low miR-34c-3p expression promote invasion and migration of non-small cell lung cancer by upregulating integrin alpha2beta1. *Signal Transduct Target Ther*. 2020;5:39.
47. Duan W, Xu Y, Dong Y, et al. Ectopic expression of miR-34a enhances radiosensitivity of non-small cell lung cancer cells, partly by suppressing the LyGDI signaling pathway. *J Radiat Res*. 2013;54:611–619.
48. Cortez MA, Valdecanas D, Niknam S, et al. In vivo delivery of miR-34a sensitizes lung tumors to radiation through RAD51 regulation. *Molecular Therapy - Nucleic Acids*. 2015;4:e270.
49. He X, Yang A, McDonald DG, et al. miR-34a modulates ionizing radiation-induced senescence in lung cancer cells. *Oncotarget*. 2017;8:69797–69807.
50. Balca-Silva J, Sousa Neves S, Goncalves C, et al. Effect of miR-34b overexpression on the radiosensitivity of non-small cell lung cancer cell lines. *Anticancer Res*. 2012;32:1603–1609.
51. Ashrafizadeh M, Zarrabi A, Hushmandi K, et al. Lung cancer cells and their sensitivity/resistance to cisplatin chemotherapy: role of microRNAs and upstream mediators. *Cell Signal*. 2021;78:109871.

52. Kulda V, Svaton M, Mukensnabl P, et al. Predictive relevance of miR-34a, miR-224 and miR-342 in patients with advanced squamous cell carcinoma of the lung undergoing palliative chemotherapy. *Oncol Lett*. 2018;15:592–599.
53. Song C, Lu P, Sun G, et al. miR-34a sensitizes lung cancer cells to cisplatin via p53/miR-34a/MYCN axis. *Biochem Bioph Res Co*. 2017;482:22–27.
54. Jiao P, Hou J, Yao M, et al. SNHG14 silencing suppresses the progression and promotes cisplatin sensitivity in non-small cell lung cancer. *Biomed Pharmacother*. 2019;117:109164.
55. Yu G, Zhong N, Chen G, et al. Downregulation of PEBP4, a target of miR-34a, sensitizes drug-resistant lung cancer cells. *Tumor Biology*. 2014;35:10341–10349.
56. Luo S, Shen M, Chen H, et al. Long non-coding RNA TP73-AS1 accelerates the progression and cisplatin resistance of non-small cell lung cancer by upregulating the expression of TRIM29 via competitively targeting microRNA-34a-5p. *Mol Med Rep*. 2020;22:3822–3832.
57. Yang X, Sun Q, Song Y, et al. circHUWE1 exerts an oncogenic role in inducing DDP-resistant NSCLC progression depending on the regulation of miR-34a-5p/TNFAIP8. *Int J Genomics*. 2021;2021:1–20.
58. Yang L, Lei C, Zhao Y, et al. MicroRNA-34c-3p target inhibiting NOTCH1 suppresses chemosensitivity and metastasis of non-small cell lung cancer. *J Int Med Res*. 2020;48: 030006052090484.
59. Catuogno S, Cerchia L, Romano G, et al. miR-34c may protect lung cancer cells from paclitaxel-induced apoptosis. *Oncogene*. 2013;32:341–351.
60. Hossian AKMN, Zahra FT, Poudel S, et al. Advanced bioinformatic analysis and pathway prediction of NSCLC cells upon cisplatin resistance. *Sci Rep*. 2021;11:6520.
61. Stahlhut C, Slack FJ. Combinatorial action of microRNAslet-7 and miR-34 effectively synergizes with erlotinib to suppress non-small cell lung cancer cell proliferation. *Cell Cycle*. 2015; 14:2171–2180.
62. Hassanein SS, Ibrahim SA, Abdel-Mawgood AL. Cell behavior of non-small cell lung cancer Is at EGFR and microRNAs hands. *Int J Mol Sci*. 2021;22:12496.
63. Ma X, Liang A, Liu Y. Research progress on the relationship between lung cancer drug-resistance and microRNAs. *J Cancer*. 2019;10:6865–6875.
64. Zhao J, Guerrero A, Kelnar K, et al. Synergy between next generation EGFR tyrosine kinase inhibitors and miR-34a in the inhibition of non-small cell lung cancer. *Lung Cancer*. 2017;108: 96–102.
65. Zhao J, Kelnar K, Bader AG. In-depth analysis shows synergy between erlotinib and miR-34a. *PLoS One*. 2014;9:e89105.
66. Zhou J, Chen X, Zhao J, et al. MicroRNA-34a overcomes HGF-mediated gefitinib resistance in EGFR mutant lung cancer cells partly by targeting MET. *Cancer Lett*. 2014;351:265–271.
67. Fu Y, Li C, Luo Y, et al. Silencing of long non-coding RNA MIAT sensitizes lung cancer cells to gefitinib by epigenetically regulating miR-34a. *Front Pharmacol*. 2018;9:82.
68. Xiong R, Sun XX, Wu HR, et al. Mechanism research of miR-34a regulates Axl in non-small-cell lung cancer with gefitinib-acquired resistance. *Thorac Cancer*. 2020;11:156–165.
69. Zheng F, Li J, Ma C, et al. Novel regulation of miR-34a-5p and HOTAIR by the combination of berberine and gefitinib leading to inhibition of EMT in human lung cancer. *J Cell Mol Med*. 2020;24:5578–5592.
70. Zhang D, Yang Y, Kang Y, et al. Dysregulated expression of microRNA involved in resistance to osimertinib in EGFR mutant non-small cell lung cancer cells. *J Thorac Dis*. 2023;15: 1978–1993.
71. Zhong S, Golpon H, Zardo P, et al. miRNAs in lung cancer. A systematic review identifies predictive and prognostic miRNA candidates for precision medicine in lung cancer. *Transl Res*. 2021;230:164–196.
72. Cortez MA, Ivan C, Valdecanas D, et al. PDL1 regulation by p53 via miR-34. *JNCI: J Natl Cancer Inst*. 2015;108:djv303.
73. Qiao X, Zhao F. Long non-coding RNA Opa interacting protein 5-antisense RNA 1 binds to micorRNA-34a to upregulate oncogenic PD-L1 in non-small cell lung cancer. *Bioengineered*. 2022;13:9264–9273.
74. Kang DY, Sp N, Jo ES, et al. The inhibitory mechanisms of tumor PD-L1 expression by natural bioactive gallic acid in non-small-cell lung cancer (NSCLC) cells. *Cancers*. 2020;12:727.
75. Kang DY, Park S, Song KS, et al. Anticancer effects of 6-gingerol through downregulating iron transport and PD-L1 expression in non-small cell lung cancer cells. *Cells*. 2023;12: 2628.
76. Shadbad MA, Ghorbaninezhad F, Hassanian H, et al. A scoping review on the significance of programmed death-ligand 1-inhibiting microRNAs in non-small cell lung treatment: a single-cell RNA sequencing-based study. *Front Med (Lausanne)*. 2022;9:1027758.
77. Hu H, Cheng R, Wang Y, et al. Oncogenic KRAS signaling drives evasion of innate immune surveillance in lung adenocarcinoma by activating CD47. *J Clin Invest*. 2023;133: e153470.
78. Arora S, Singh P, Ahmad S, et al. Comprehensive integrative analysis reveals the association of KLF4 with macrophage infiltration and polarization in lung cancer microenvironment. *Cells*. 2021;10:2091.
79. Agostini M, Knight RA. miR-34: from bench to bedside. *Oncotarget*. 2014;5:872–881.
80. Beg MS, Brenner AJ, Sachdev J, et al. Phase I study of MRX34, a liposomal miR-34a mimic, administered twice weekly in patients with advanced solid tumors. *Invest New Drug*. 2017;35:180–188.
81. Hong DS, Kang YK, Borad M, et al. Phase 1 study of MRX34, a liposomal miR-34a mimic, in patients with advanced solid tumours. *Br J Cancer*. 2020;122:1630–1637.
82. Li WJ, Wang Y, Liu R, et al. MicroRNA-34a: potent tumor suppressor, cancer stem cell inhibitor, and potential anticancer therapeutic. *Front Cell Dev Biol*. 2021;9:640587.
83. Rupaimoole R, Yoon B, Zhang WC, et al. A high-throughput small molecule screen identifies ouabain as synergistic with miR-34a in killing lung cancer cells. *iScience*. 2020;23: 100878–100878.
84. Fu J, Imani S, Wu M, et al. MicroRNA-34 family in cancers: role, mechanism, and therapeutic potential. *Cancers*. 2023;15: 4723.


 