JBACHS
Journal of Basic and Clinical Health Sciences

J Basic Clin Health Sci 2025: 9; 205-211
https://doi.org/10.30621/jbachs.1595106
RESEARCH ARTICLE

INVESTIGATION OF EPIDERMAL GROWTH FACTOR RECEPTOR PATHWAY RELATED, EXOSOMAL miRNAS IN NON-SMALL CELL LUNG CANCER CASES

Altug Koc[1], Asim Leblebici[1], Haydar Soydane Karakus[2], Ceyda Aldag[2], Kadri Murat Erdogan[3], Merve Saka Guvenc[3], Su Ozgur[4], Tuncay Goksel[2,4], Yasemin Basbinar[5]

[1]Department of Translational Oncology, Institute of Health Sciences, Dokuz Eylul University, Izmir, Turkey.
[2]Department of Pulmonary Medicine, Faculty of Medicine, Ege University, Izmir, Turkey.
[3]Genetic Evaluation Center, Tepecik Training and Research Hospital, Health Sciences University, Izmir, Turkey.
[4]EgeSAM-Ege University Translational Pulmonary Research Center, Izmir, Turkey.
[5]Department of Translational Oncology, Institute of Oncology, Dokuz Eylul University, Izmir, Turkey.

ORCID: A.K. 0000-0002-8366-6806; A.L.0000-0002-5197-6631; H.S.K.0000-0002-3099-9172; C.A.0000-0003-3130-4739; K.M.E. 0000-0003-0097-1424; M.S.G.0000-0001-8842-0381; S.O. 0000-0002-8993-674X; T.G.0000-0002-6089-1840; Y.B. 0000-0001-9439-2217

Corresponding author: Altug Koc, **E-mail:** draltug@gmail.com
Received: 02.12.2024; **Accepted:** 19.01.2025; **Available Online Date:** 31.01.2025

Cite this article as: Koc A, Leblebici A, Karakus HS, Aldag C, Erdogan KM, Guvenc S, Ozgur S, Goksel T, Basbınar Y. Investigation of Epidermal Growth Factor Receptor Pathway Related, Exosomal miRNAs in Non-Small Cell Lung Cancer Cases. J Basic Clin Health Sci 2025; 9: 205-2011.

ABSTRACT

Purpose: The Epidermal Growth Factor Receptor (EGFR) gene and its associated pathways have recently emerged as promising targets in precision medicine for Non-Small Cell Lung Cancer (NSCLC). This study serves as a proof of concept, leveraging exosomal miRNAs as a cost-effective and minimally invasive liquid biopsy method. We aim to investigate four exosomal miRNAs: miR-22-3p, miR-221-3p, miR-30b and miR-30c and with miR-1288 serving as control. These miRNAs have been previously defined in the literature.
Materials and Methods: A total of thirty-six samples from distinct Non-Small Cell Lung Cancer (NSCLC) cases are included. Exosomes are derived from the patients' plasma, followed by miRNA isolation, cDNA synthesis, and quantitative polymerase chain reactions. The Δ/Δ Ct approach is employed for quantification of miRNAs.
Results: The controls: miRNA and miR-1288 are expressed in almost all samples. One sample is an exception. The two target miRNAs, miR-30c and miR-22-3p, generated successful polymerase chain reaction (PCR) curves. However, the remaining two miRNAs, miR-221-3p and miR-30b produced PCR curves with low amplitude.
Conclusion: miR-30b, miR-30c, miR-221-3p, miR-22-3p have previously been reported to be associated with lung cancer, but they have not been studied in a patient series until now. In our study, exosomal miR-22-3p and miR-30c were isolated from the cancer patients' plasma, suggesting that they could serve as potential lung cancer biomarkers.

Keywords: EGFR, exosome, liquid biopsy, miRNA, Non-Small Cell Lung Cancer (NSCLC).

INTRODUCTION

Among the world, lung cancer is the leading cause cancer related deaths. World Health Organization reported the incidence for lung cancer cases is about 2 million per year (1). In Turkey, the incidence is 29,314. Majority of those cases are male patients and the mean age of patients at the time of lung cancer diagnosis is 60. The 80.7% of them have Non-Small Cell Lung Cancer (NSCLC) type. At the time of diagnosis, about 47% of them are in the advanced

stage (2). Patients diagnosed at an early stage have a chance of cure with surgery, but patients diagnosed at a late stage do not have this chance. Therefore, new treatment approaches are needed.

Emerging therapeutic approaches are being developed to address the genetic profile of tumors. In clinical settings, key biomarkers for NSCLC are the driver mutations associated with the EGFR, KRAS, ALK, ROS1 and MET genes. About 15% of NSCLC patients have mutations in the Epidermal Growth Factor Receptor (EGFR) gene. Exon 19 deletions and the L858R mutation of EGFR enhance the tyrosine kinase activity. Medications such as erlotinib, gefitinib, and afatinib, which target these EGFR mutations, improve progression-free survival (3). However, in 50% of cases, additional EGFR mutations (such as T790M) lead to drug resistance (4). Examining EGFR mutations has become a standard procedure in advanced-stage NSCLC cases. Somatic EGFR mutations need to be monitored intermittently throughout the cancer process and the genetic profile in different metastatic foci needs to be determined. Liquid biopsy has provided the answer to this need.

Liquid biopsy, includes four main concepts: Extracellular Vesicles (EVs), Tumor-educated platelets (TEPs), Circulating tumor cells (CTCs), Cell-free DNA (cfDNA). Exosomes are subclass of EVs, and they are stable in plasma (5). Exosomes are membrane vesicles and they are 40-150 nm in diameter. Exosomes may be detected in plasma, ascites and other body fluids and. Recent studies suggest that those vesicles function as communicators between tumor cells and far body sites. Exosomes released by tumors contribute to tumor progression and play key roles in immunomodulation, angiogenesis, and drug resistance (6). They transport active genetic material, with miRNA notably influencing the pre-metastatic niche (7). It is proposed that exosomal miRNAs may have relations with EGFR variants, making them potential biomarkers for NSCLC cases (8). Thus, we aim to examine four miRNAs associated with the exosomal EGFR pathway in metastatic NSCLC patients tested for EGFR variants through liquid biopsy.

MATERIALS AND METHODS

Participants

Four miRNA targets associated with the EGFR pathway were used for analysis: miR-221-3p, miR-22-3p miR-30b and miR-30c. The miR-1228 and the housekeeping gene SNORD48 were analyzed as internal controls. Patients diagnosed with advanced stage NSCLC participated in the study. EGFR somatic mutation research results of solid biopsy samples taken at the time of diagnosis and liquid biopsy samples taken during follow-up are used in the study. Since there are no guidelines regarding the sampling criteria and when liquid biopsy samples should be taken during routine patient follow-up, the results of available liquid biopsy samples are used.

Study Group

The study group included NSCLC patients who underwent EGFR mutation testing via liquid/solid biopsies and were managed at the Department of Pulmonary Medicine, Ege University Hospital, and the Genetic Evaluation Center, Tepecik Training and Research Hospital. The study has been approved by the ethics committee of Dokuz Eylul University, Non-invasive Clinical Research Ethical Committee (Date: 13.02.2019, Decision no: 2019/03-72).

RNA Isolation and Sample Collection

Blood samples were collected from 36 cases, and plasma was separated within 24 hours. Plasma samples were kept at -80°C until exosome extraction. Sequentially, exosome extraction, miRNA isolation (50 µL total), and cDNA synthesis were performed using commercial kits as per the manufacturers' protocols [Midi Kit for Plasma/Serum Exosome Purification and RNA Isolation (58500), Norgen, Canada].

Quantitative Polymerase Chain Reaction (Q-PCR)

The cDNA samples are diluted to a concentration 80 times lower than the original. PCR reactions are carried out using the “LightCycler® 480 SYBR Green I Master” (Roche Molecular Systems, USA) along with specific primers targeting the desired miRNAs and reference genes. The Δ/ΔCt approach is applied to normalize the Ct values of miRNAs and perform relative quantification (9).

Statistical Analysis

The statistical analyses were performed to assess the frequency and distribution of mutations detected in solid and liquid biopsies, as well as the association between mutation status and patient response to targeted therapies. Descriptive statistics, including frequencies and percentages, were used to

summarize categorical data. Continuous variables were analyzed using mean and standard deviation values where applicable. For the evaluation of mutation prevalence in solid biopsies, the data revealed a significant distribution across different mutation types. Chi-square tests were employed to determine whether the observed differences in mutation frequencies (e.g., Exon 19 deletion, Exon 21 mutation, and combined mutations) were statistically significant. Similarly, comparisons were made between the mutation detection rates in solid biopsies and the first liquid biopsies to evaluate concordance and sensitivity. A second liquid biopsy is performed in patients with decreased response to targeted therapy to investigate the presence of mutations associated with drug resistance. In cases requiring a second liquid biopsy, mutation dynamics were analyzed to assess the emergence of drug resistance-associated mutations. The proportional differences in mutation detection rates between the first and second liquid biopsies were evaluated using Fisher's exact test, given the small sample size. This approach allowed for robust statistical evaluation of the emergence of T790M mutations and other resistance-related genetic alterations. All statistical analyses were conducted using [software name, e.g., SPSS, R], and a p-value of <0.05 was considered statistically significant. Results are reported with 95% confidence intervals to ensure the reliability of the findings.

RESULTS

The descriptive characteristics of 36 patients are as follows: Twenty males (55.6%) males and 16 females (44.4%). The mean age of the patients was 60.1±11.7 and the median was 58.0 [38.0-85.0]. When the distribution of patients according to smoking status is evaluated: 11.1% (n=4) are smokers (active smokers), 19.4% (n=7) are non-smokers, and 25.0% (n=9) are ex-smokers (former smokers). When the distribution of patients according to survival status is evaluated: 33.3% (n=12) are dead and 30.6% (n=11) are alive (Table I). The patient samples are previously investigated for somatic, driver EGFR mutations as routine workup of NSCLC cases by Roche Cobas (USA) system according to the producer's recommendations.

When the mutation detection status of the patients in solid biopsy is evaluated: No mutation is detected in 47.2% (n=17) of the cases, Exon 19 deletion is detected in 36.1% (n=13) of the cases, Exon 21 mutation in 5.6% (n=2), Exon 19 deletion and L858R mutation in 8.3% (n=3). In the first liquid biopsy of patients, Exon 19 deletion mutation is detected in 8.3% (n=3) of the cases, Exon 20 insertion is detected in 2.8% (n=1), and no mutation is detected in 88.9% of the cases. In the second liquid biopsy of patients Exon 19 deletion is found in 25.0% (n=1), Exon 19 deletion and T790M mutation in 50.0% (n=2), and Exon 20 insertion in 25.0% (n=1) of patients (Table 1). While there are 13 cases in which Exon 19 deletion is detected in solid biopsy; and 2 of these cases could be detected in the first liquid biopsy (Table 2).

Table 1. Descriptive characteristics of 36 patients.

	No	**%**
Gender		
Male	20	55.6
Female	16	44.4
Total	36	100.0
	Median ± SD	**Median [min-max]**
Age	60.1±11.7	58.0 [38.0-85.0]
Smoking Status		
Unknown	16	44.4
Ex smoker	9	25.0
Non-smoker	7	19.4
Smoker	4	11.1
Total	36	100.0
Survival		
Death	12	33.3
Alive	11	30.6
Unknown	13	36.1
Total	36	100.0
Solid Biopsy Result		
No mutation	17	47.2
Exon19 deletion	13	36.1
Exon 21	2	5.6
Exon 20 insertion	1	2.8
Exon 19 deletion & L858R	3	8.3
Total	36	100.0
Liquid Biopsy (first)		
Exon 19 deletion & T790M	3	8.3
Exon 20 insertion	1	2.8
No mutation	27	88.9
Total	31	100.0
Liquid Biopsy (second)		
Exon 19 deletion	1	25.0
Exon 19 deletion & T790M	2	50.0
Exon 20 insertion	1	25.0
Total	4	100.0

Table 2. The mutation status of patients by solid biopsy and first liquid biopsy.

Solid Biopsy Results and First Liquid Biopsy Results, Crosstabulation						
			Liquid Bx 1			Total n (%)
			Exon 19 deletion and T790M n (%)	Exon 20 insertion n (%)	No mutation n (%)	
Solid Biopsy	Exon 19 deletion n (%)	n	2	0	11	13
		% within Solid Biopsy	15.4%	0.0%	84.6%	100.0%
		% within First Liquid Biopsy	66.7%	0.0%	34.4%	36.1%
	Exon 19 deletion and L858R mutation n (%)	n	0	0	3	3
		% within Solid Biopsy	0.0%	0.0%	100.0%	100.0%
		% within First Liquid Biopsy	0.0%	0.0%	9.4%	8.3%
	Exon 20 insertion n (%)	n	0	1	0	1
		% within Solid Biopsy	0.0%	100.0%	0.0%	100.0%
		% within First Liquid Biopsy	0.0%	100.0%	0.0%	2.8%
	Exon 21 mutation n (%)	n	0	0	2	2
		% within Solid Biopsy	0.0%	0.0%	100.0%	100.0%
		% within First Liquid Biopsy	0.0%	0.0%	6.3%	5.6%
	No mutation (%)	n	1	0	16	17
		% within Solid Biopsy	5.9%	0.0%	94.1%	100.0%
		% within First Liquid Biopsy	33.3%	0.0%	50.0%	47.2%
Total n (%)		n	3	1	32	36
		% within Solid Biopsy	8.3%	2.8%	88.9%	100.0%
		% within First Liquid Biopsy	100.0%	100.0%	100.0%	100.0%

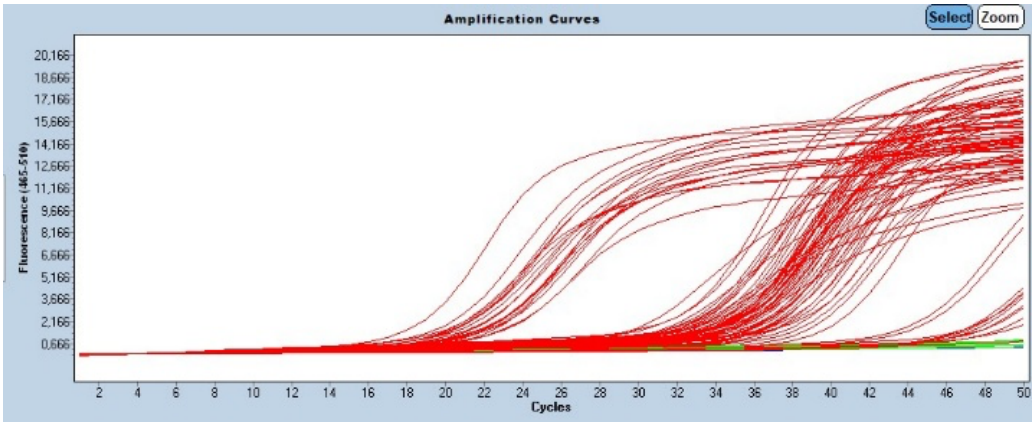

Figure 1. Amplification curves of the control and target probes. The control probe miR1288 has Ct values between 16-21 cycles (left side). The mean Ct values for miR-22-3p and miR-30c are 30.8 and 38.4, respectively (center panel). In contrast, two of the miRNAs, miR-221-3p and miR-30b, exhibit low PCR amplification curves, with Ct values exceeding 40 (right panel).

The control miR1288 was identified in every sample, except for one, whereas SNORD48 did not amplify in seven samples. This indicates that miR1288 is a reliable Q-PCR control. Two target miRNAs, miR-221-3p and miR-30b, yield insufficient PCR amplicons. Because of the limited quantity of extracted miRNA (50 µL), these targets cannot be reassessed and are therefore excluded from the study. The remaining miRNAs, miR-22-3p and miR-30c, generate PCR amplification curves, with average Ct values of 30.8 for miR-22-3p and 38.4 for miR-30c (Figure 1).

Among the samples analyzed, four cases showing amplification for miR-22-3p and miR-30c also exhibit EGFR mutations in their initial liquid biopsy: Three cases involve exon 19 deletions combined with the T790M mutation, and one case presents with an exon 20 insertion.

DISCUSSION

The EGFR gene is the most widely investigated target for personalized new therapies in routine oncology practice. Drug-sensitive and resistant variants are determining the management of NSCLC cases (11-13). Academic research is also focused on EGFR-related pathways and looking for genetic and epigenetic variations (14-15). Tumor tissues from the solid biopsies have the advantage great amount of tumor DNA but the disadvantages are also present: Resampling and simultaneous monitorization of tumor genotype evolution in all metastatic foci are almost impossible in most of the NSCLC cases. Monitorization is mandatory to realize the therapeutic targets. Therefore, the liquid biopsies from tumor-derived molecules such as ctDNA in the plasma get their role in clinical management. Moreover, other liquid biopsy techniques are emerging. One of them is based on EVs.

miRNAs are promising targets due to their potential as predictive biomarkers and their prospective role as therapeutic agents. Recently, several miRNAs have been investigated in the context of lung cancer, including microRNA-133b, microRNA-135, miR-181a, miR-223, microRNA-155, microRNA-200c, miR-30a-5p, microRNA-106a, miR-26a, miRNA-212, miR-486-5p, miR-3127-5p, miR-130a, miR-138-5p, microRNA-137, and the cluster miR-134/487b/655 (16–32).

Two of the targeted miRNAs, namely miR-221-3p and miR-30b, are omitted from the study. We consider that if the first miRNA isolate is adequate, we may have the opportunity to get proper PCR curves for them also. Starting with a minimum 100ul miRNA sample, would make a difference in success rates because of the exclusive lung cancer patient group, most of the time it is not possible to resample. SNORD48 does not appear to be an appropriate control for exosomal miRNA research, but miR1288 just failed in one sample so it could be preferred as a control.

A comprehensive study with 845 cases of EGFR mutation status of lung adenocarcinoma patients from our region is previously reported elsewhere (10). Therefore, the presented study does not focus on EGFR mutations but briefly: The most frequent EGFR mutation is exon 19 deletion in our study group, and it is found in 36.1% of solid biopsies, 8.3% of first liquid biopsies and 25% of second biopsies (Table II). The distinct positive mutation rates seem to be related to patient selection for testing. Because the same laboratory and methods are used for all samples (Roche Cobas, California, USA).

CONCLUSION

As a conclusion, in literature, EVs and miRNAs are investigated as potential promising biomarkers separately because of the challenging patient group, microvesicle, miRNA extraction, and Q-PCR protocols. Extracellular vesicles (EVs) carry a representative sample of cancer cell contents, including miRNAs (5), making exosomal miRNAs clinically significant. In our proof-of-concept study, exosomal miR-30c and miR-22-3p were successfully isolated from the NSCLC cases' plasma in a cost-effective manner, highlighting their potential as biomarkers for these patients. Among the cases analyzed, four exhibit EGFR mutations, with average Ct values of 30.8 for miR-22-3p and 38.4 for miR-30c. These values are comparable to those from non-mutant samples and fall within acceptable ranges for routine laboratory use. We consider that the investigation of the presented and recently reported lung cancer-associated miRNAs by our approach in exosomes would reveal a clinically significant genotype-phenotype correlation in NSCLC cases (16-32).

Acknowledgements: None.

Author Contributions: Design: AK, TG, YB. Supervision: HS, TG, YB. Data Collection and Processing: AK, AL, HS, CA, KME, MSG, SO. Analysis and/or Interpretation: AK, AL, HS, CA, KME, MSG, SO. Literature Review: AK, KME, MSG, SO. Writing: AK, SO. Critical Review: AK, TG, YB. Conception: AK, TG, YB. Fundings: TG, YB. Materials: AK.

Conflict of Interest: The authors declare that there is no conflict of interest for the presented study. The authors alone are responsible for the content and writing of this article.

Ethical Approval: This study has been approved by the ethics committee of Dokuz Eylul University, Non-invasive Clinical Research Ethical Committee (Date: 13.02.2019, Decision no: 2019/03-72).

Funding: The study was supported by Dokuz Eylul University, Scientific Research Coordination Unit (Project Number: TDK-2021-2611).

Peer-review: Externally peer-reviewed.

REFERENCES

1. Sabaila A, Fauconnier A, Huchon C. Chimiothérapie intrapéritonéale pressurisée en aérosol (CIPPA): Une nouvelle voie d'administration dans les carcinoses péritonéales d'origine ovarienne. Gynecol Obstet Fertil 2015;43:66–67.
2. Tuncay Goksel, Sultan Eser, Salih Z. Guclu, et al. Turkish Lung Cancer Mapping Project Study Group. Prognostic factors affecting survival in cases with lung cancer [A lung cancer mapping project in Turkey (LCMPT)]. In: European Respiratory Journal 2013. p. P2920.
3. Lee CK, Brown C, Gralla RJ, et al. Impact of EGFR Inhibitor in Non–Small Cell Lung Cancer on Progression-Free and Overall Survival: A Meta-Analysis. JNCI J Natl Cancer Inst 2013;105:595–605.
4. Onozato R, Kosaka T, Kuwano H, Sekido Y, Yatabe Y, Mitsudomi T. Activation of MET by gene amplification or by splice mutations deleting the juxtamembrane domain in primary resected lung cancers. J Thorac Oncol 2009;4:5–11.
5. Reclusa P, Sirera R, Araujo A, et al. Exosomes genetic cargo in lung cancer: A truly Pandora's box. Vol. 5. Translational Lung Cancer Research 2016;p. 483–491.
6. Taverna S, Giallombardo M, Gil-Bazo I, et al. Exosomes isolation and characterization in serum is feasible in non-small cell lung cancer patients: Critical analysis of evidence and potential role in clinical practice. Oncotarget 2016;7:28748–28760.
7. Nuzhat Z, Kinhal V, Sharma S, Rice GE, Joshi V, Salomon C. Tumour-derived exosomes as a signature of pancreatic cancer- liquid biopsies as indicators of tumor progression. Oncotarget. 2017.
8. Rolfo C, Chacartegui J, Giallombardo M, Alessandro R, Peeters M. Exosomes isolated in plasma of non-small cell lung cancer patients contain microRNA related to the EGFR pathway: Proof of concept. J Thorac Oncol 2016;11:S85.
9. Livak KJ, Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the 2-ΔΔCT method. Methods 2001;25:402–408.
10. Ermin S, Batum Ö, Saka Güvenç M, Diniz G, Ayrancı A, Erdoğan KM, et al. The relation between distant metastasis and genetic change type in stage IV lung adenocarcinoma patients at diagnosis. Clin Respir J 2021;15:196–202.
11. Poh M-E, Liam C-K, Rajadurai P, Chai C-S. Epithelial-to-mesenchymal transition (EMT) causes acquired resistance to afatinib in a patient with epidermal growth factor receptor (EGFR)-mutant lung adenocarcinoma. J Thorac Dis 2018;10:E560–563.
12. Bach D-H, Luu T-T-T, Kim D, et al. BMP4 Upregulation Is Associated with Acquired Drug Resistance and Fatty Acid Metabolism in EGFR-Mutant Non-Small-Cell Lung Cancer Cells. Mol Ther Nucleic Acids 2018;12:817–828.
13. Lyu H, Han A, Polsdofer E, Liu S, Liu B. Understanding the biology of HER3 receptor as a therapeutic target in human cancer. Acta Pharm Sin B 2018;8:503–510.
14. Kharbanda A, Rajabi H, Jin C, Alam M, Wong K-K, Kufe D. MUC1-C confers EMT and KRAS independence in mutant KRAS lung cancer cells. Oncotarget 2014;5:8893–8905.
15. Park K-S, Raffeld M, Moon YW, et al. CRIPTO1 expression in EGFR-mutant NSCLC elicits intrinsic EGFR-inhibitor resistance. J Clin Invest 2014;124:3003–3015.
16. Li B, Ding C-M, Li Y-X, Peng J-C, Geng N, Qin W-W. Over-regulation of microRNA-133b inhibits cell proliferation of cisplatin-induced non-small cell lung cancer cells through PI3K/Akt and JAK2/STAT3 signaling pathways by targeting EGFR. Oncol Rep 2018;39:1227–1234.
17. Wang N, Zhang T. Downregulation of MicroRNA-135 Promotes Sensitivity of Non-Small Cell Lung Cancer to Gefitinib by Targeting TRIM16. Oncol Res 2018;26:1005–1014.
18. Iaboni M, Russo V, Fontanella R, et al. Aptamer-miRNA-212 Conjugate Sensitizes NSCLC Cells to TRAIL. Mol Ther Nucleic Acids 2016;5:e289.
19. Pang W, Tian X, Bai F, et al. Pim-1 kinase is a target of miR-486-5p and eukaryotic translation initiation factor 4E and plays a critical role in lung cancer. Mol Cancer 2014;13:240.
20. Sun Y, Chen C, Zhang P, et al. Reduced miR-3127-5p expression promotes NSCLC proliferation/invasion and contributes to dasatinib sensitivity via the c-Abl/Ras/ERK pathway. Sci Rep 2014;4:6527.
21. Zhou Y-M, Liu J, Sun W. MiR-130a overcomes gefitinib resistance by targeting met in non-small cell lung cancer cell lines. Asian Pac J Cancer Prev 2014;15:1391–1396.

22. Gao Y, Fan X, Li W, Ping W, Deng Y, Fu X. miR-138-5p reverses gefitinib resistance in non-small cell lung cancer cells via negatively regulating G protein-coupled receptor 124. Biochem Biophys Res Commun 2014;446:179–186.
23. Li P, Ma L, Zhang Y, Ji F, Jin F. MicroRNA-137 down-regulates KIT and inhibits small cell lung cancer cell proliferation. Biomed Pharmacother 2014;68:7–12.
24. Kitamura K, Seike M, Okano T, et al. MiR-134/487b/655 cluster regulates TGF-β-induced epithelial-mesenchymal transition and drug resistance to gefitinib by targeting MAGI2 in lung adenocarcinoma cells. Mol Cancer Ther 2014;13:444–453.
25. Ping W, Gao Y, Fan X, Li W, Deng Y, Fu X. MiR-181a contributes gefitinib resistance in non-small cell lung cancer cells by targeting GAS7. Biochem Biophys Res Commun 2018;495:2482–2489.
26. Zhang H, Chen F, He Y, et al. Sensitivity of non-small cell lung cancer to erlotinib is regulated by the Notch/miR-223/FBXW7 pathway. Biosci Rep 2017;37:BSR20160478.
27. Liu Q, Yu Z, Yuan S et al. Circulating exosomal microRNAs as prognostic biomarkers for non-small-cell lung cancer. Oncotarget 2017;8:13048–13058.
28. Narita M, Shimura E, Nagasawa A, et al. Chronic treatment of non-small-cell lung cancer cells with gefitinib leads to an epigenetic loss of epithelial properties associated with reductions in microRNA-155 and -200c. Chai KX, editor. PLoS One 2017;12:e0172115.
29. Sato H, Shien K, Tomida S, et al. Targeting the miR-200c/LIN28B axis in acquired EGFR-TKI resistance non-small cell lung cancer cells harboring EMT features. Sci Rep 2017;7:40847.
30. Jin X, Chen Y, Chen H, et al. Evaluation of tumor-derived exosomal miRNA as potential diagnostic biomarkers for early-stage non-small cell lung cancer using next-generation sequencing. Clin Cancer Res 2017;23:5311–5319.
31. Rothschild SI, Gautschi O, Batliner J, Gugger M, Fey MF, Tschan MP. MicroRNA-106a targets autophagy and enhances sensitivity of lung cancer cells to Src inhibitors. Lung Cancer 2017;107:73–83.
32. Xu S, Wang T, Yang Z, et al. miR-26a desensitizes non-small cell lung cancer cells to tyrosine kinase inhibitors by targeting PTPN13. Oncotarget 2016;7:45687–45701.