E-ISSN:2454-9894 P-ISSN: 2454-9886
International Archives of
BioMedical and Clinical Research
(An Official Publication of "Ibn Sina Academy of Medieval Medicine & Sciences")
WWW.IABCR.ORG

Review Article

Micro RNAs and Non-Small Cell Lung Cancer

Mirza Masroor[1*], Amit Jain[2*], Tayyaba Fatma[1], Anant Mohan[3], Alpana Saxena[1]

[1]Department of Biochemistry, Maulana Azad Medical College and Associated Hospitals, New Delhi, India. [2]Dr Baba Saheb Ambedakar Medical College, Delhi, India. [3]All India Institute of Medical Science, New Delhi, India.
(equal contribution of author)*

ABSTRACT

Non-small cell lung cancer is a major leading cause of cancer related death and its late diagnosis/prognosis, accounting for the high rate of mortality. Presences of circulating microRNAs (miRNAs) in body fluids represent stable and reproducible bio markers for several solid tumors, including non-small cell lung cancer. Micro RNAs have been categorized as oncogenic microRNAs and "tumor suppressor micro RNAs" and miRNAs activities may provide exciting opportunities for early cancer detection. There is an urgent need to find a less invasive and a more reliable biomarker which can increase the probability of early non-small cell lung cancer detection.

Key words: *Non-small Cell Lung Cancer, Circulating miRNAs, Tumor suppressor miRNAs, Oncogenic miRNAs*

INTRODUCTION

Globally cancer is a medical and socioeconomic threat for most of the developed as well as developing country, despite molecular management of disease, molecular based screening, targeted tyrosine kinase inhibitors (TKI) and chemotherapeutics, and our increased understanding of the molecular basis pathogenesis of tumor occurrence, progression and resistance of disease. As our moves into the advancement in cancer management, advanced understanding of cancer risk and cancer heterogeneity will be primary focus to get success in early detection, management and new targeted drugs or therapies. There is urgent need to improve the understanding of molecular mechanisms and identify reliable and potential biomarkers involved in the occurrence of Non-Small cell lung cancer which could be used disease monitoring as accuracy in diagnosis, prediction of prognosis, disease progression and response to therapy used in patients' treatment. In the past two decades, researchers have identified non-coding genetic components of the human genome, such as microRNAs (miRNAs), as central role in organ development and human disease[1] and one of the most promising molecular entity in cancer research since the first miRNA gene called as lin-4 was identified and discovered in Caenorhabditis elegans.[2] Several other microRNA have been identified and so far over 2500 microRNAs have been described in the human genome miRBase (www.mirbase.org)[3] Micro RNAs are 22-nucleotide long non-coding RNAs (ncRNAs) which regulates negative post-transcription of gene through binding to promoter mainly 3' untranslated open reading frames (ORFs).[4-8] microRNAs (miRNAs) have been given more focus as cancer biomarkers. This non coding small miRNAs involved in many physiological and pathological processes due to their ability to regulate the human genes expression. It was shown that miRNAs are very specific to cancer and classifies human cancers.[9,10] Recently, an increasing number of reports have implicated a role for miRNAs in lung cancer progression.[11,12] MicroRNAs are potential targets for treating NSCLC[13] and research has focused on the diagnostic and prognostic potential of different microRNAs (miRNAs) in NSCLC. It is believed that miRNA expression is an important in NSCLC occurrence.[14,15] Evidence shows that miRNAs are grossly dysregulated in human cancers, including NSCLC, and

Access this article online	
Website: www.iabcr.org	Quick Response code
DOI: 10.21276/iabcr.2016.2.3.1	

Received:03.07.16| **Revised**:12.08.16| **Accepted**:22.08.16

Corresponding Author
Mirza Masroor, Department of Biochemistry, Maulana Azad Medical College and Associated Hospitals, New Delhi, India

Copyright: © the author(s) and publisher. IABCR is an official publication of Ibn Sina Academy of Medieval Medicine & Sciences, registered in 2001 under Indian Trusts Act, 1882. This is an open access article distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

may serve as oncogenes or tumour suppressors.[16] Recent studies have shown that not only can miRNAs be used to sub-classify NSCLCs[17] but specific miRNA profiles may also predict prognosis and disease recurrence in early-stage NSCLCs.[18,19,14,20,21]

Biogenesis of miRNA and its functions:

MicroRNA genes are specifically much conserved located between the introns or exons of protein-coding genes and in intergenic sequences.[22] MicroRNA genes are transcribed by mainely RNA polymerase II into long primary miRNAs (pri-miRNAs) that is kilobase-long primary miRNA transcripts (pri-miRNAs) and 5'caped and 3' end polyadenylated. Pri-miRNAs are subsequently cleaved into ~60-110 nucleotide-long precursor miRNAs (pre miRNAs) by the nuclear microprocessor complex including RNase III Drosha, DiGeorge syndrome critical region gene 8 (DGCR8) and pasha proteins by "cropping" process. The average length of human pre-miRNA is 33-base-pair long forms hairpin stem, a terminal loop, and at upstream two single-stranded flanking regions and downstream of the hairpin structure. Pre-miRNAs next to cytoplasm exported by the exportin-5/Ran GTPase complex, where miRNAs undergo maturation.[23-25] RNaseIII Dicer-1 enzyme, TRBP/PACT proteins complex cleaves cytoplasmic pre-miRNAs into 17-24 nucleotide long duplex miRNAs which are separated by helicase enzyme. The two separated strands are "passenger" and "guide" strand, which the passenger strand is degraded and the latter on guide strand associated with Ago protein activates RISC, resulting in mRNA degradation or translational inhibition, depending on the percentage of sequence complementarity between the miRNA 5'-seed sequence and mRNA 3'-UTR element.[26,27] In a recent study by Suzuki et al, demonstrated that p53 interacts with the Drosha microprocessor complex through DEAD-box RNA helicase p68 (DDX5) and activates the processing of pri-miRNAs into mature pre-miRNAs.[28] The p53-mediated post transcriptional maturation of miRNAs, linking the core tumour suppressor p53 to the miRNA biogenesis pathway[28]. These findings may provide an evidence for the widespread miRNA down regulation observed in human cancers, in which p53 is often dysfunctional.[29] Available data indicate that miRNAs play significant roles in tumorigenesis, metastasis and drugs responsiveness can be investigative biomarkers for lung carcinoma.[30,31]

Source of MicroRNA:

Current research has been focused on micro RNA and it was found that the miRNAs detected not only in tumor tissues but also in body fluids and even in some extracellular organelles. Differences in level of miRNAs in tumor tissues and normal tissues have been extensively studied and collected data showed that miRNAs are involved in lung cancer occurrence, spread of disease and drug response. Takamizawa et al identified that the cytosolic miRNA family, let-7 which was associated with the tumorigenesis of lung cancer and observed that introducing let-7a and let-7f isoforms into lung adenocarcinoma cell line A549 with low baseline levels of let-7 expression, significantly inhibited the growth of A549 cells.[32] Where it was observed that patients with reduced let-7 expression significantly shorter patient survival after diagnosis.[32] Several other cytosolic miRNAs such as miR-17–92[33-36], miR-200 family of miR- NAs (miR-200a, miR-200b, miR-200c, miR-141, and miR-429)[37], miR-125a-3p/5p[38], miR-21[39], and miR-106b-25 cluster (miR-106b and miR-93) have been reported to play pivotal role in tumorigenesis and metastases of lung cancer.[40]

Some other cytosolic microRNAs also involved in drugs response and resistance down-regulation of miR-17-5p expression was associated with paclitaxel resistance by up-regulation of the autophagic protein Beclin 1 (BECN1) expression in NSCLC[41]. Similarly, let-7a, miR-126, and miR-145 could sensitize the responsiveness of the large-cell cancer cell line H460 and A549 cells to Gefitinib.[42] MicroRNAs are also found in body fluids such as blood, serum, plasma, urine, cerebrospinal fluid (CSF), sputum, saliva, and broncho alveolar lavage (BAL).[43,44] Several studies indicate that body fluid miRNAs are more stable even under extreme conditions, such as repeated freeze-thaw and at extreme pH (e.g., pH=1 or pH=13). This feature makes body fluid miRNAs suitable biomarkers for diagnosis and prognosis of disease.[45] Several other miRNAs such as miR-141, miR-155, miR-1254, and miR-574-5p, were identified as potential early diagnostic biomarkers.[46,47] A recent meta-analysis indicated that the early diagnostic value of circulating miR-21 is much better than the plasma miR-21.[48] Roth et al. found that circulating levels of miR-361-3p and miR-625 could be used as blood-based biomarkers for differentiating malignant lung tumors other than benign lung tumors.[49] Boeri et al showed that plasma levels of miR-155, miR-197, and miR-182 could serve as non-invasive biomarkers for early detection and diagnosis of lung cancer50. These miRNAs were shown to be significantly elevated in the plasma of the lung cancer patients compared to the cancer free control subjects by greater than 10-folds, and could help discriminate the two groups.[50] Several studies demonstrated that expression of miRNAs is also observed in extracellular vesical (exosomes) is different in the normal condition and in pathological conditions such as tumor. Exosomal miRNAs are encapsulated in the cell organelles called the exosomes, which are small (30–90 nm) extracellular vesicles derived from the multivesicular body (MVB) sorting pathway.[51] Six miRNAs has been identified (miR-151a-5p, miR- 30a-3p, miR-200b-5p, miR-629, miR-100, and miR-154-3p) for segregating lung adenocarcinoma patients and lung granuloma patients.[52] Rabinowits et al. compare 12 specific miRNAs (miR-17-3p, miR-21, miR-106a, miR-146, miR-155, miR-191, miR-192, miR- 203, miR-205, miR-210, miR-212, and miR-214) in circulating exosomes, lung cancer patient's tissue and healthy people.[53] The results showed that there was no significant difference in exosomes derived miRNA and

tissues, and suggested could be used as biomarkers for lung cancer.[54] (Rabinowits G et al., 2009).

MicroRNAs in Lung Cancer:

Lung cancer is most frequently occurred, low survival and high relapse of disease observed,[55,56,57] invasion and metastases is the main factors responsible for NSCLC treatment failure and drug resistance.[58,59] MicroRNAs play a critical role as oncogenes and tumor suppressors and directly involved in several kinds of haematological and solid tumors,[60] Single miRNA regulates hundreds of downstream signalling pathways,[61] and influence several cell regulatory processes, including cellular development, differentiation, proliferation, cell death, and metabolism. Researchers analysed and found strong correlation to confirm that the aberrant expression of miRNAs in cancer patients compared to healthy individual had significant role in cancer development.[62,63] Tang et al. found that miRs-21, 145 and 155 could be a non-invasive screening tool in the early detection of lung cancer.[64] A panel of four plasma microR¬NAs (mir-486, -30d, -1 and -499) was also found to be associated with good and poor prognosis of NSCLC patients.[61] In NSCLC patients it was found that reduced let-7 gene expression correlated with poor prognosis of disease[32,18],[62-64] and a single nucleotide polymorphism in let-7 complementary site 6 of the K-RAS mRNA at 3'-UTR is significantly associated with increased NSCLC risk these observations suggest a role for let-7 family miRNAs as tumour suppressors.[65] The miR-17-92 cluster is overexpressed in small-cell lung cancer.[66] Ebi et al also confirmed the relationship the association of miR-17-92 overexpression with RB inactivation and concluded miR-17-92 miRNA cluster may be a potential therapeutic target in lung cancer.[67]

MicroRNAs in Non-Small Lung Cancer:

Fact is that desperately we need more accurate diagnosis, prognosis, effective treatment method and additional genetic biomarkers, such as miRNAs, could be more promising tool in patients' management and treatment plan for Non-small cell lung cancer. It has been identified that miR-34c, miR-183, and miR-210 showed significantly altered expression in lung adenocarcinoma.[68] It has been seen that still mostly NSCLC cases are diagnosed in late stages due to the lack of early diagnostic methods[47]. It was found that MiR-125a-3p and miR-125a-5p down-regulated in NSCLC patients could be a predictive tool to identify tumor invasion and lymph node metastasis. The miRNA-128b down regulation was also found to be associated with high EGFR expression and a consequently better survival observed in NSCLC patients treated with gefitinib.[69,70] Bahl et al found that miR-21, miR-486, miR-375, and miR-200b showed a significantly different expression in Non-small Cell Lung adenocarcinoma patients versus normal subjects in early detection of lung adenocarcinoma.[71] Jun Osugi et al proposed that upregulation of miR-210 is a prognostic factor in patients with lung adenocarcinoma and cancer relapse upregulation of miR-210 expression found to be a positive prognostic factor for disease-free survival in NSCLC patients,[72] Recently Eilertsen et al also reported that the potential prognostic role of miR-210 in NSCLC patients.[73] In lung adenocarcinoma patients' miR-99b and miR-102 showed higher expression levels, as well as adenocarcinoma patients with increased miR-155 and decreased let-7a-2 expression had worse patients' survival18. Increased expression of miR-708 in never smoker lung adenocarcinoma was also seen to be associated with worse patients overall survival.[74] It was also found that miR-34c function as a tumor suppressor and miR-183, miR-210 have a potential oncogenic role and could be a diagnostic and prognostic marker in lung adenocarcinoma68 as well as miR-210 positively regulate glycolytic pathway in order to enhance rapid tumor growth.[75] Several studies have shown that tumor suppressors nature of let-7 family miRNAs play key role in regulation of cell survival and proliferation in lung carcinoma.[76,18,32,77,78,79] Esquela et al and Trang et al also reported intranasal administration of a let-7 reduces tumor growth into lung cancer xenograft models and found to be significantly associated.[80,81] Above data suggest that let-7 replacement therapy is indeed and may be promising therapeutic treatment in Lung cancers.

MicroRNA as Tumor Suppressor and Oncogene:

Several miRNAs found to be functioned as tumor suppressors when their stopped function or loss of function could contribute to normal cell transformation into cancerous cell. Functionally inactive miRNA could be due to several mechanisms such as deletion, mutation of nucleotide, epigenetic silencing or hypermethylation and alteration in miRNA processing.[82,83,84] It has been found that let-7 family of miRNAs is a typical tumor suppressor and found to be downregulated in several cancers including lung cancer.[18] Let-7 family members miRNA actively inhibit the mRNAs of well-characterized oncogenes such as RAS,[85,86] HMGA2[87] and c-Myc.[88] There are other miR-29 family members have been shown to be downregulated in lung cancer.[89] He L et al in 2007 observed that miR-34 family involved in interfering the post transcriptional regulation of p53 and found that overexpression of miR-34 family members regulates apoptosis and cell cycle arrest.[90] It was also found that miR-34 block tumor growth in the mouse model of non-small cell lung cancer[76] and in a study Min GP demonstrated miR-34c member of miR-34 family may act as a potential tumor suppressor.[91] It was observed that miRNAs 126, 145 associated with lung cancer suppression and found to be down regulated in Lung Cancer, it showed that miRNAs -126, 145 act as a tumor suppressor and pro-apoptotic.[92,93,94] Most importantly Boutros et al revealed that expression of miRNAs platform is more finely regulated than those of proteins expression.[95] Several studies also observed that MicroRNAs had oncogenic behaviour and found to be higher expression in cancers, Zhang et al 60 suggested that several miRNAs are directly involved in lung, breast, brain, liver, colon cancer, and leukaemia, specific miRNAs can be

useful diagnostic and prognostic biomarkers.[96] MicroRNA-182 is most important miRNA found to be upregulated in Non-small Cell Lung cancers.[97] It was observed that MicroRNA-182 has oncogenic nature which increases cellular proliferation and was found to be associated with drug resistance.[98,99] MicroRNA-183 belongs to one of the unique miRNAs showed potential oncogenic role in lung adenocarcinoma.[100] It was also found that overexpression of miR-183 is associated with worse overall survival of Lung Cancer patients.[101] Xu et al also suggested that miR-183 high expression in female lung adenocarcinoma involved with lymph node metastasis, disease progression, worse overall and progression free survival.[102] Micro RNA-182 is an important miRNAs seen upregulated in cancers. Several researchers reported miR-182 found to be upregulated in NSCLC96. Furthermore, miR-182 functions as an oncomiR to enhance cancer cell proliferation[97,98] It was also observed that miR-182 plays an important role in drug resistance found to be upregulated in the multidrug resistant.[102] MicroRNA-17-29 family cluster (miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, miR-92-1) are oncogenes[103] and these miRNAs accelerate tumor growth and development as well as helps to promote tumour neo-vascularisation.[104,105]

CONCLUSION

So far, large segment of scientific research outcomes indicating the utility of micro RNAs as prognostic and diagnostic biomarkers for disease prediction and peer-reviewed scientific publications has been extremely useful to provide guidance for further investigations in management of deadly cancer disease. For the Investigation of cancers using minimal invasive methods easily available human samples such as saliva, urine are extremely important for the development of reliable and cost-effective miRNA based markers for routine use in early cancer diagnosis/detection and therapeutic assessment/ prognosis other than blood based investigations. Micro RNA expression profiling Lung cancer particularly NSCLC could be worthy strategy to detect disease in early stage, diagnosis, prognosis and would help in developing novel treatment strategies. Going more deep insight study on miRNA may assist in Non-small Cell Lung cancer treatment using targeted agents. Great progress has been made in the research of miRNAs and lung cancer and several miRNAs with differential expression patterns in lung cancer tissues compared to normal tissues have been identified. Furthermore, aberrant expression patterns of miRNAs in lung cancer patients can not only be detected in tumor tissues but also in body fluids and extracellular organelles such as exosomes. Overall, the study of miRNAs offers a new and exciting angle for us to understand the molecular mechanisms of lung cancer biology. Further studies could provide more accurate biomarkers for both diagnosis and prediction, as well as improved strategies for lung cancer treatment.

REFERENCES

1. Olsen PH, Ambros V (1999). The lin-4 regulatory RNA controls developmental timing in Caenorhabditis elegans by blocking LIN-14 protein synthesis after the initiation of translation. Dev Biol, 216:671–680.
2. Lee RC, Feinbaum RL, Ambros V (1993). The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell. 75:843–54.
3. Kozomara A, Griffiths-Jones S (2014). MiRBase. annotating high confidence microRNAs using deep sequencing data. potential target in the treatment of Non-Small- Cell Lung Carcinomas. Gene, 506:355–359.
4. Raponi M, Dossey L, Jatkoe T, et al (2009). MicroRNA classifiers Nucleic Acids Res; 42:D68–73.
5. Ambros V (2004). The functions of animal microRNAs. Nature, 431,350-355.
6. Bartel DP (2004). MicroRNAs: genomics, biogenesis, mechanism, and function. Cell,116, 281-97.
7. Chen K, Rajewsky N (2007). The evolution of gene regulation by transcription factors and microRNAs. Nat Rev Genet, 8, 93-103.
8. He L, Hannon GJ (2004). MicroRNAs: small RNAs with a big role in gene regulation. Nat Rev Genet, 5, 522-31.
9. Filipowicz W, Bhattacharyya SN, Sonenberg N (2008). Mechanisms of post-transcriptional regulation by microRNAs: are the answers in sight? Nat Rev Genet, 9, 102-14.
10. Lu J, Getz G, Miska EA, et al (2005). MicroRNA expression profiles classify human cancers. Nature, 435:834–838.
11. Rosenfeld N, Aharonov R, Meiri E, et al (2008). MicroRNAs accurately identify cancer tissue origin. Nat Biotechnol, 26:462–469.
12. Zhang WC, Liu J, Xu X, et al (2013).The role of microRNAs in lung cancer progression. Med Oncol, 30:675–683.
13. Saito M, Schetter AJ, Mollerup S, et al (2011). The association of microRNA expression with prognosis and progression in early-stage, non-small cell lung adenocarcinoma: a retrospective analysis of three cohorts. Clin Cancer Res, 17:1875–1882.
14. Malleter M, Jacquot C, Rousseau B, et al (2012). miRNAs, a
15. for predicting prognosis of squamous cell lung cancer. Cancer Res, 69:5776–5783.
16. Lin PY, Yu SL, Yang PC (2010). MicroRNA in lung cancer. Br J Cancer, 103(8):1144–8.
17. Croce CM (2009) Causes and consequences of microRNA dysregulation in cancer. Nat Rev Genet 10: 704–714.
18. Bishop JA, Benjamin H, Cholakh H, et al (2010). Accurate classification of non-small cell lung carcinoma using a novel microRNA-based approach. Clin Cancer Res 16: 610–619.
19. Yanaihara N, Caplen N, Bowman E, et al (2006). Unique microRNA molecular profiles in lung cancer diagnosis and prognosis. Cancer Cell 9: 189–198.
20. Yu SL, Chen HY, Chang GC, et al (2008). MicroRNA signature predicts survival and relapse in lung cancer. Cancer Cell 13: 48–57.
21. Seike M, Goto A, Okano T, et al (2009). MiR-21 is an EGFR-regulated anti-apoptotic factor in lung cancer in never-smokers. Proc Natl Acad Sci USA 106: 12085–12090.
22. Patnaik SK, Kannisto E, Knudsen S, et al (2010). Evaluation of microRNA expression profiles that may predict recurrence of localized stage I non-small cell lung cancer after surgical resection. Cancer Res 70:36–45.
23. Rodriguez A, Griffiths-Jones S, Ashurst JL, et al (2004). Identification of mammalian microRNA host genes and transcription units. Genome Res 14: 1902–1910.
24. Lee Y, Ahn C, Han J, et al (2003). The nuclear RNase III Drosha initiates microRNA processing. Nature 425: 415–419.
25. Yi R, Qin Y, Macara IG, et al (2003). Exportin-5 mediates the nuclear export of pre-microRNAs and short hairpin RNAs. Genes Dev 17: 3011– 3016.
26. Denli AM, Tops BB, Plasterk RH, et al (2004). Processing of primary microRNAs by the Microprocessor complex. Nature 432: 231–235.
27. Hammond S, Bernstein E, Beach D, et al (2000). An RNA-directed nuclease mediates post-transcriptional gene silencing in Drosophila cells. Nature 404: 293–329.

28. Diederichs S, Haber DA (2007). Dual role for argonautes in microRNA processing and posttranscriptional regulation of microRNA expression. Cell 131: 1097–1108.
29. Suzuki HI, Yamagata K, Sugimoto K, et al (2009). Modulation of microRNA processing by p53. Nature 460: 529–533.
30. Lu J, Getz G, Miska EA, et al (2005). MicroRNA expression profiles classify human cancers. Nature, 435:834–838.
31. Yanaihara N, Caplen N, Bowman E, et al (2006). Unique microRNA molecular profiles in lung cancer diagnosis and prognosis. Cancer Cell 9: 189–198.
32. Lin PY, Yu SL, Yang PC (2010). MicroRNA in lung cancer. Br J Cancer, 103(8):1144–8.
33. Takamizawa J, Konishi H, Yanagisawa K, et al (2004). Reduced expression of the let-7microRNAs in human lung cancers in association with shortened post-operative survival. Cancer Res, 64 (11):3753–6.
34. Liu B, Peng XC, Zheng XL, et al (2009). 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.
35. Crawford M, Brawner E, Batte K, et al (2008). MicroRNA-126 inhibits invasion in non-small cell lung carcinoma cell lines. Biochem Biophys Res Commun, 373(4):607–12.
36. Feller SM (2001). Crk family adaptors- signalling complex formation and biological roles. Oncogene 20(44):6348–71.
37. Kobashigawa Y, Sakai M, NaitoM, et al (2007). Structural basis for the transforming activity of human cancer- related signaling adaptor protein CRK. Nat Struct Mol Biol 14(6):503–10.
38. Gibbons DL, Lin W, Creighton CJ, et al (2009). Contextual extracellular cues promote tumor cell EMT and metastasis by regulating miR-200 family expression. Genes Dev, 23(18):2140–51.
39. Jiang L, Huang Q, Zhang S, et al (2010). Hsa-miR-125a- 3p and hsa-miR-125a-5p are down regulated in non-small cell lung cancer and have inverse effects on invasion and migration of lung cancer cells. BMC Cancer, 10:318.
40. Zhang JG, Wang JJ, Zhao F, et al (2010). MicroRNA-21(miR-21) represses tumor suppressor PTEN and promotes growth and invasion in non- small cell lung cancer (NSCLC). Clin Chim Acta, 411(11–12):846–52.
41. Savita U, Karunagaran D (2013). MicroRNA- 106b-25 cluster targets b-TRCP2, increases the expression of Snail and enhances cell migration and invasion in H1299 (non-small cell lung cancer) cells. Biochem Biophys Res Commun, 434(4):841–7.
42. Chatterjee A, Chattopadhyay D, Chakrabarti G (2014). miR-17-5p down regulation con- tributes to paclitaxel resistance of lung cancer cells through altering beclin1 expression. PLoS One, 9(4):e95716.
43. Zhong M, Ma X, Sun C, et al (2010). Micro RNAs reduce tumor growth and contribute to enhance cytotoxicity induced by gefitinib in non-small cell lung cancer. Chem Biol Interact (2010) 84(3):431–8.
44. Steeg PS (2003). Metastasis suppressors alter the signal transduction of cancer cells. Nat Rev Cancer, 3(1):55–63.
45. Huang J, Song H, Liu B, et al (2013). Expression of Notch-1 and its clinical significance in different histological subtypes of human lung adenocarcinoma. J Exp Clin Cancer Res, 32:84.
46. Mitchell PS, Parkin RK, Kroh EM, et al (2008). Circulating microRNAs as stable blood-based markers for cancer detection. Proc Natl Acad Sci USA. 105:10513–8.
47. Roth C, Kasimir- Bauer S, Pantel K, et al (2011). Screening for circulating nucleic acids and caspase activity in the peripheral blood as potential diagnostic tools in lung cancer. Mol Oncol, 5(3):281–91.
48. Foss KM, Sima C, Ugolini D, et al (2011). MiR-1254 and miR-574-5p: serum-based micro RNA biomarkers for early-stage non- small cell lung cancer. J Thorac Oncol, 6:482–8.
49. Chang L, Youping D, Leilei W, et al (2013). Early diagnostic value of circu- lating MiRNA-21in lung cancer: a meta-analysis. Tsinghua Sci Technol, 18(5):441–5.
50. Roth C, Stuckrath I, Pantel K, et al (2012). Low levels of cell-free circulating miR-361-3p and miR-625*as blood-based mark- ers for discriminating malignant from benign lung tumors. PLoSOne 7(6):e38248.
51. Boeri M, Verri C, Conte D (2011). MicroRNA signatures in tissues and cancer. Cancer Imaging 6:9–12.
52. Hu G, Drescher KM, Chen XM (2012). Exosomal miRNAs: biological properties and therapeutic potential. Front Genet, 3:56.
53. Cazzoli R, Buttitta F, DiNicola M, et al (2013). MicroRNAs derived from circulating exosomes as non-invasive biomarkers for screening and diagnose lung cancer. J Thorac Oncol, 8(9):1156–62.
54. Rabinowits G, Gercel-Taylor C, Day JM, et al (2009). Exosomal microRNA: a diagnostic marker for lung cancer. Clin Lung Cancer, 10:42–6.Rabinowits G, Gercel-Taylor C, Day JM, et al (2009). Exosomal microRNA: a diagnostic marker for lung cancer. Clin Lung Cancer, 10:42–6.
55. Subramaniam S, Thakur RK, Yadav VK, et al (2013). Lung cancer biomarkers: state of the art. J Carcinog. ; 12:3.
56. Hayano T, Garg M, Yin D, et al (2013). SOX7 is downregulated in lung cancer. J Exp Clin Cancer Res,32:17.
57. Mac Donagh L, Gray SG, Finn SP, et al (2014). The emerging role of microRNAs in resistance to lung cancer treatments. Cancer Treat Rev,41(2):160–9.
58. Steeg PS (2003). Metastasis suppressors alter the signal transduction of cancer cells. Nat Rev Cancer, 3(1):55–63.
59. Huang J, Song H, Liu B, et al (2013). Expression of Notch-1 and its clinical significance in different histological subtypes of human lung adenocarcinoma. J Exp Clin Cancer Res, 32:84.
60. Zhang B, Pan X, Cobb GP, et al (2007). microRNAs as oncogenes and tumor suppressors. Dev Biol, 302(1):1–12.
61. Hu Z, Chen X, Zhao Y, et al (2010). Serum microRNA signatures identified in a genome-wide serum microRNA expression profiling predict survival of non-small-cell lung cancer. J Clin Oncol, 28(10):1721–6.
62. Bi CL, Chng WJ (2011). miRNA deregulation in multiple myeloma. Chin Med J (Engl), 124:3164–3169.
63. Wu DG, Wang YY, Fan LG, et al (2011). MicroRNA-7 regulates glioblastoma cell invasion via targeting focal adhesion kinase expression. Chin Med J (Engl), 124:2616–2621.
64. Tang D, Shen Y, Wang M, et al (2013). Identification of plasma microRNAs as novel noninvasive biomarkers for early detection of lung cancer. Eur J Cancer Prev, 22:540–548.
65. Chin LJ, Ratner E, Leng S, et al (2008). A SNP in a let-7 microRNA complementary site in the KRAS 3' untranslated region increases non-small cell lung cancer risk. Cancer Res 68: 8535–8540.
66. Hayashita Y, Osada H, Tatematsu Y, et al (2005). A polycistronic microRNA cluster, miR-17-92, is overexpressed in human lung cancers and enhances cell proliferation. Cancer Res 65: 9628–9632.
67. Ebi H, Sato T, Sugito N, Hosono Y, et al (2009). Counter balance between RB inactivation and miR-17-92 overexpression in reactive oxygen species and DNA damage induction in lung cancers. Oncogene 28: 3371–3379.
68. Min GP, Chang HL, Woo JL, et al (2015). Unique microRNAs in lung adenocarcinoma groups according to major TKI sensitive EGFR mutation status. Diagnostic Pathology, 10:99.
69. Joshi S, Kotecha S (2007). Lung growth and development. Early Hum Dev, 83, 789-94.
70. Kozuki T, Hisamoto A, Tabata M, et al (2007). Mutation of the epidermal growth factor receptor gene in the development of adenocarcinoma of the lung. Lung Cancer, 58, 30-5.
71. Bahl A, Sharma DN, Rath GK, et al (2008). Small molecular inhibitor of transforming growth factor-beta protects against development of radiation-induced lung injury. Int J Radiat Oncol Biol Phys, 72, 630.
72. Jun O, Yuka K, Yuki O, et al (2015). Prognostic Impact of Hypoxia-Inducible miRNA-210 in Patients with Lung Adenocarcinoma. Journal of Oncology 10.1155/2015/316745.
73. Eilertsen S. Andersen S. Al-Saad, et al (2014). "Positive prognostic impact of miR-210 in non-small cell lung cancer," Lung Cancer, 272–278.
74. Jang JS, Jeon HS, Sun Z, et al (2012). Increased miR-708 pression in NSCLC and its association with poor survival in lung adenocarcinoma from never smokers. Clin Cancer Res. 18 (13):3658–67.
75. Devlin C, Greco S, Martelli F, et al (2011). miR-210: More than a silent player in hypoxia. IUBMB Life. 63(2):94–100.
76. Trang P, Wiggins JF, Daige CL, et al (2011). Systemic delivery of tumor suppressor microRNA mimics using a neutral lipid

emulsion inhibits lung tumors in mice. Mol. Ther. 19, 1116–1122.
77. Johnson CD, Esquela KA, Stefani G, et al (2007). The let-7 microRNA represses cell proliferation pathways in human cells. Cancer Res, 67, 7713–7722.
78. Kumar MS, Erkeland SJ, Pester RE, Chen, et al (2008). Suppression of non-small cell lung tumor development by the let-7 microRNA family. Proc. Natl. Acad. Sci. USA, 105, 3903–3908.
79. He XY, Chen JX, Zhang Z, et al (2010). The let-7a microRNA protects from growth of lung carcinoma by suppression of k-Ras and c-Myc in nude mice. J. Cancer Res. Clin. Oncol, 136, 1023–1028.
80. Esquela-KA, Trang P, Wiggins JF, et al (2008). The let-7 microRNA reduces tumor growth in mouse models of lung cancer. Cell Cycle, 7, 759–764.
81. Trang P, Medina PP, Wiggins JF, et al (2010). Regression of murine lung tumors by the let-7 microRNA. Oncogene, 29, 1580–1587.
82. Calin GA, Dumitru CD, Shimizu M, et al (2002). Frequent deletions and down-regulation of micro- RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. Proc Natl Acad Sci USA, 99:15524–15529.
83. Nakamura T, Canaani E, Croce CM (2007). Oncogenic All1 fusion proteins target Drosha-mediated microRNA processing. Proc Natl Acad Sci USA, 104:10980–10985.
84. Saito Y, Liang G, Egger G, et al (2006). Specific activation of microRNA-127 with downregulation of the proto-oncogene BCL6 by chromatin-modifying drugs in human cancer cells. Cancer Cell, 9:435–443.
85. Johnson SM, Grosshans H, Shingara J, et al (2005). RAS is regulated by the let-7 microRNA family. Cell, 120:635–647.
86. Akao Y, Nakagawa Y, Naoe T (2006). let-7 microRNA functions as a potential growth suppressor in human colon cancer cells. Biol Pharm Bull, 29:903–906.
87. Lee YS, Dutta A (2007). The tumor suppressor microRNA let-7 represses the HMGA2 oncogene. Genes Dev, 21:1025–1030.
88. Sampson VB, Rong NH, Han J, et al (2007). MicroRNA let-7a down-regulates MYC and reverts, Cancer Res.67(20):9762-70.
89. Iorio MV, Ferracin M, Liu CG, et al (2005). MicroRNA gene expression deregulation in human breast cancer. Cancer Res, 65:7065–7070.
90. He L, He X, Lim LP, et al (2007). A microRNA component of the p53 tumour suppressor network. Nature, 447:1130–1134.\
91. Min GP, Chang HL, Woo JL, et al (2015). Unique microRNAs in lung adenocarcinoma groups according to major TKI sensitive EGFR mutation status. Diagnostic Pathology, 10:99.
92. Bhaskaran M, Wang Y, Zhang H, et al (2009). MicroRNA-127 modulates fetal lung development. Physiol Genomics, 37, 268-78.
93. Liu J, Lu KH, Liu ZL, et al (2012a). MicroRNA-100 is a potential molecular marker of non-small cell lung cancer and functions as a tumor suppressor by targeting polo-like kinase 1. BMC Cancer, 12, 519.
94. Kesanakurti D, Maddirela DR, Chittivelu S, et al (2013). Suppression of tumor cell invasiveness and in vivo tumor growth by microRNA-874 in non-small cell lung cancer. Biochem Biophys Res Commun, 434, 627-33.
95. Boutros PC, Lau SK, Pintilie M, et al (2009). Prognostic gene signatures for non-small-cell lung cancer. Proc Natl Acad Sci U S A. 106(8):2824–8.
96. Shen J, Stass SA, Jiang F (2013). MicroRNAs as potential biomarkers in human solid tumors. Cancer Lett. 329(2):125–36.
97. Guan P, Yin Z, Li X, et al (2012). Meta-analysis of human lung cancer microRNA expression profiling studies comparing cancer tissues with normal tissues. J Exp Clin Cancer Res, 31:54.
98. Yang WB, Chen PH, Hsu TS, et al (2014). Sp1-mediated microRNA-182 expression regulates lung cancer progression. Oncotarget, 5(3):740–753.
99. Wang M, Wang Y, Zang W, et al (2014) Downregulation of microRNA-182 inhibits cell growth and invasion by targeting programmed cell death 4 in human lung adenocarcinoma cells. Tumour Biol, 35(1):39–46.
100. Cho WC, Chow AS, Au JS (2009). Restoration of tumour suppressor hsa-miR-145 inhibits cancer cell growth in lung adenocarcinoma patients with epidermal growth factor receptor mutation. Eur J Cancer. 45(12):2197–206.
101. Zhu W, Liu X, He J, et al (2011). Overexpression of members of the microRNA-183 family is a risk factor for lung cancer: a case control study. BMC Cancer,11:393-2407-11-393.
102. Xu F, Zhang H, Su Y, et al (2014). Up-regulation ofmicroRNA-183-3p is a potent prognostic marker for lung adenocarcinoma of female non-smokers. Clin Transl Oncol.16(11):980–5.
103. Husted S, Sokilde R, Rask L, et al (2011). MicroRNA expression profiles associated with development of drug resistance in Ehrlich ascites tumor cells. Mol Pharm, 8(6):2055–2062.
104. He L, Thomson JM, Hemann MT, et al (2005). A microRNA polycistron as a potential human oncogene. Nature 435: 828–833.
105. O'Donnell KA, Wentzel EA, Zeller KI, et al (2005). c-Mycregulated microRNAs modulate E2F1 expression. Nature 435: 839 –843.
106. Dews M, Homayouni A, Yu D, et al (2006). Augmentation of tumor angiogenesis by a Myc-activated microRNA cluster. Nat Genet 38: 1060–1065.

How to cite this article: Masroor M, Jain A, Fatma T, Mohan A, Saxena A. Micro RNAs and Non-small Cell Lung Cancer. Int Arch BioMed Clin Res. 2016;2(3):1-6**.** DOI: 10.21276/iabcr.2016.2.2.6

Source of Support: Nil, **Conflict of Interest:** None