Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 8 [9] August 2019 : 01-08

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD
Global Impact Factor 0.876
Universal Impact Factor 0.9804
NAAS Rating 4.95

REVIEW ARTICLE **OPEN ACCESS**

MicroRNAs in Lung Cancer tissues and Pleural fluids: A Review

Anees Muhammad[1], Najeeb Ullah[2], Habib Ullah Khan[3], Muhammad Jaseem Khan[4]
[1]Research Assistant,Department of MLT, University of Haripur, Pakistan
[2]Assistant Professor, Institute of Biotechnology and Genetics Engineering, Agricultural University Peshawar
[3]Incharge PCR Lab, Department of Pathology, Khyber Teaching Hospital, Medical Teaching Institution, Pakistan
[4]Assistant Professor, Institute of Paramedical Sciences, Khyber Medical University, Peshawar
Corresponding author's Email: jaseem.ipms@kmu.edu.pk

ABSTRACT
Lung cancers are one of a leading cause of death in smokers and healthy individuals. The earlier screening and diagnosis of lung cancers is essential for the therapeutic purposes. The miRs can detect in different biological specimens of lung cancer patients. Present review was concentrate on miRs as a diagnostic biomarkers in lung cancer tissues and other body fluid. All the published articles in different international journals wereretrieve from search engines by using terms such as "miRs as biomarker in lung cancer" from 2011-2018. All the relevant articles about lung cancer microRNAs were included. Data analyzed were through Microsoft excel 2016. Several articles were retrieve from various data banks, only twenty seven articles were found relevant to present review in which twenty four were of tissues, two of pleural fluid and one of bronchoalveolar lavage fluids. Hundreds of miRs were dysregulated but 38 were significantly up or down regulated in reported studies. Out of total 38, only six miRs were consistently dysregulated in various studies that are mir-96, mir-183, mir-196a, mir-205, mir-29 and mir-21 in whichmir-96, mir-183, mir-196a, mir-205 and mir-21 were upregulated while mir-29 were downregulted in various studies whereas only single hsa-let-7b-5p were inconsistently reported by two different studies. It is concluded with the result of present review that significantly dysregulated miRs have a crucial role in early diagnosis regarding the therapeutic purpose of lung cancer.
Key words: *Lung cancer, miRs, biomarkers, tissues*

Received 19.05.2019 Revised 20.06.2019 Accepted 19.07. 2019

INTRODUCTION

Globally, lung cancer remains one of the leading cancer of death among cancers. Increasing the morbidity and mortality rate from past few decades due to different etiological factors such as pollution, aging, unhygienic environment and consumption of various carcinogens (1). It is accepted that lung cancer is a fatal disease due to complex mechanism of carcinogenesis; unfavorable consequences occur [2]. In early stages, lung cancer patients remains asymptomatic which leads to extremely intense condition due to non-accessibility of reliable diagnosis and effective curative treatment(3). Almost 1.5 million new cases diagnose each year of lung cancer. Most frequent among all cancers and only 5 years survival rate is about 10%. The resolving cases also rely on timely detection and identification of lung cancer significantly(4). Approximately, 75% of lung cancers are detected at metastatic and progressive stages as a result less survival rate (5). Different risk factors are associated with lung cancer such as age gender, occupation, status, susceptibility to ionizing radiation, cigarette smoking, exposure to environmental carcinogenic chemical and air pollution(6). Due to miserable lifestyle, the occurrence of lung cancers are incessantly increasing on each successive day especially in developing countries due to insufficiency of precise, accurate and early diagnostic techniques(6). Early diagnosis of lung cancer can be achieved by developing an advanced approach on immediate effort [1, 7]. Currently, diagnosis of lung cancer based on imaging technology like Computer Tomography (CT), bronchoscopy, biopsies and other molecular biomarker (growth factor receptor) but until no blood tests are primarily effective [1, 8]. The crucial strategy for identification, diagnosis and treatments are requisite of lung cancer [1].

Recently, the breakthrough of microRNAs (miR) opened a new era for prediction of diagnosis and therapeutic response to medication in lung cancer [9]. MicroRNAs (miR) as the name indicates, the small (19-22 nucleotides), non-coding endogenous RNAs, involved in a numerous crucial biological function such as modulating the expression of desire genes, cell cycle, cell proliferation and apoptosis. Reports revealed that there is essential role of miR in cancer genetics, tumorgenesis and their progression. Thus, miR is an effective and excellent nominee for diagnosis and therapeutic purpose in cancer [10]. Additionally, miR have both tumor suppressive function as well as oncogenic activity [11]. First miR was discovered in early 1993 and at the moment miR are exists naturally in both animals and plants [12]. Until now, numbers of miRs are under debate but different studies predict that about one thousand are present in human genome.

It is reported that about 2-5% of human genes are comprised of MicroRNAs [13]. It is found that cancer affected cells release higher concentration of miRNAs than unaffected cells [1]. Furthermore, miRs have high stability rate in different biological specimens (plasma, serum and pleural fluids) because shows resistance to pH, repeated thaw procedure, high temperature, exogenous and endogenous RNAs(14). The mechanism are diverse and complex therefore it is expensive and time consuming technique [7].It is reported that altered expression of miR has been detected in different physiological and pathological conditions like infections and cancer (pancreatic, prostate, lung, oral, gastric, esophageal, breast, leukemia, liver and others) [11. 14]. Moreover, higher concentration of miR are observed in diverse samples (tissues, blood, serum and plasma) of cancers individuals as compared to healthy control group [1, 13]. The detection of miR level in samples could be reliable and accurate biomarkers [14]. The miRs are detected in lung cancer as they are dysregulated in pathological conditions, types and in different stages of lung cancer patients and can be determined in affected lung tissues [15].

Although many numbers of studies has been done by several researcher and growing rapidly in recent years. To overcome the inconsistency, present study are conducted to find the coherence in different reports about the miRs expression and to estimate the diagnostic value of different miRs in lung cancer tissues. Up to now, study on a large scale of miR expression in lung cancer tissues as biomarkers are not reported. This type of review explores the useful biomarkers for early diagnosis and therapeutic purpose of lung cancer.

MATERIALS AND METHODS

The original published data were extracted from Google, Google scholar, Pubmed and NCBI database on lung cancer tissue with standard protocol, covering approximately all published articles from 2011 to 2018 in international journals. Different words and terms were used for data collection such as "microRNAs as biomarkers in lung cancer patients", "miRs for a diagnostic purpose in lung cancer tissue", "miR in lung cancers". All the collected data were specifically related to microRNAs in lung cancer tissues, pleural and broncho-alveolar lavage fluid of lung cancer patients with a limitation of language barrier. Eligibility of studies must follow the following criteria: miRs expression in lung cancer patients, tissue sample taken from resected lung tumor, mentioned the sample size including both control and cases irrespective of type and stage of lung cancer. Hence, all the miRs expression in blood, serum, urine, sputum and plasma of lung cancer patients were excluded.

The information obtained from published article was the following: last name of first author, date of publication, setting of research, total number of lung cancer cases and healthy control, journal of publication, specimen and significant miRs. Additionally, list of dysregulation (UP and Down) of miRs features and the pattern of sensitivity and specificity were also obtained from published materials. The Microsoft Excel sheet 2016 was used for analysis of data.

RESULT AND DISCUSSION

Hundreds of articleswere retrieve from different data bases, which was related to miRs expression in lung cancers but many were excluded due to irrelevancy with the current study. The excluded data were belonging to microRNAs expression in lung cancer in other specimen (sputum, serum, plasma etc) than tissues, pleural and broncho alveolar lavage. According to the above mentioned criteria, only 27 articles found for current review, in which 24 of tissues sample whereas 2 of pleural specimen and only 1 of broncho alveolar lavage from 2011 to 2018 were included in present report. All the studies occur in different region of the world but majority of studies were conducted in China in last few years.

Different detection methodology was used in which the RT-PCR and qRT-PCR were frequently used method. The number of patients investigated ranged from case study to 216 including controls group participants. Present data comprised 1938 lung cancers cases and 1060 control participants. Total of 38

microRNAs were significantly dysregulated in all included data in which seven are repeated in different reports as shown in table No.1 and 3.

The following miRs including mir-96, mir-182, mir-183, mir-328, mir-196, mir-29b, mir-511, mir-1297, mir-93, mir-205, mir-221, mir-let-7e, mir-650, mir-135b, mir-375, mir-136, mir-493, mir-141, mir-224, mir-218, mir-425, mir-486-5p, mir-30a-5p, mir-21, mir-155, mir-188, mir-hsa-let-7f-5p, mir-let-7b-5p, mir-30, mir-148a, mir-378, hsa-mir-circ RNA-103827, hsa-mir-circRNA-000122, mir-198, mir-134, mir-185, mir-22 and mir-17-92 cluster were noted in reported articles as shown in table No.2 and 4. Out of total dysregulated miRs, seven miRs were significantly up or downregulated including mir-96, mir-183, mir-196a, mir-29, mir-205, mir-21 and mir-let-7b-5p reported. Out of 38 miRs, 12 were down-regulated (mir-29b, mir-205, mir-221, mir-let7e, mir-34b, mir-493, mir-218, mir-486-5p, mir-30a-5p, mir-30d, mir-29a and mir-122) whereas remaining twenty four are up regulated. Moreover, only single hsa-mir-let-7b-5p are both up and down regulated, reported by two different authors.

After critical analysis, it is found that mir-96 was upregulated in two studies (108,120), high expression of mir-183 in three studies, mir-196a increased expression in two reports, mir-29 downregulated in two studies and overexpression of mir-205 in two reports while inconsistency were noted in mir-let-7b-5p that is dysregulated in two studies but upregulated reported by Hossaini et al. and Fazio et.al observed downregulated as shown in table No.1 and 2.

Table No.1: (A) Reported MicroRNAs in Lung Cancer tissues from 2011 to 2018

Authors	Region	Cases/ control	Specimen	References
Zhu et al. (2011)	China	70/70	Tissue & sera	(16)
Arora et al. (2011)	USA	39/NA	Tissue	(17)
Liu et al. (2012)	China	34/34	Tissue	(18)
Rothschild et al. (2012)	USA	84/NA	Tissue	(19)
Zhang et al. (2012)	China	NA/NA	tissue	(20)
Yong et al. (2012)	China	105/105	Tissue & sera	(21)
Jia et al. (2013)	China	96/96	Tissue	(22)
Wen et al. (2013)	Taiwan	case study	Tissue	(23)
Hamamoto et al. (2013)	Japan	86/86	Tissue	(24)
Shen et al. (2014)	China	37/37	Tissue	(25)
Edmonds et al. (2014)	USA	20/14	Tissue	(26)
Gu1 et al. (2014)	China	65/65	Tissue	(27)
Zhang et al. (2015)	China	125/125	Tissue	(7)
Cuia et al. (2015)	USA	145/145	Tissue	(28)
Wang et al. (2015)	China	57/19	Tissue	(29)
Zhu et al. (2015)	China	44/44	Tissue	(30)
Wang et al. (2017)	China	216/NA	Tissue	(31)
Gallach et al. (2017)	Spain	210/32	Tissue	(32)
Fazio et al. (2017)	Germany	18/4	Tissue	(33)
Hosseini et al. (2017)	Tehran	24/10	Tissue	(34)
Yang et al. (2017)	China	76/76	Tissue	(35)
JI et al. (2018)	China	42/NA	Tissue	(36)
Liu et al. (2018)	China	38/38	Tissue	(37)
Xu et al. (2018)	China	43/43	Tissue	(38)

Table No.2: Reported MicroRNAs in Lung Cancer tissues from 2011 to 2018

Significant MicroRNAs	Expression (UP/Down)	References
miR-96, miR-182, and miR-183	Upregulated	(16)
miR-328	Upregulated	(17)
miR-196a	Upregulated	(18)
miR-29b	Downregulated	(19)
miR-511- and miR-1297	Upregulated	(20)
miR-93, miR-205, miR-221 and let-7e	Up miR-93 and miR-205 miR-221 and let-7e Down	(21)
miR-650	Upregulated	(22)
miR-135b	Upregulated	(23)
hsa-miR-196b, hsa-miR-205 and hsa-miR-375	Upregulated	(24)
miR-136	Upregulated	(25)
miR-96 and -183	mir-96 & mir-183 Up miR-34b downregulated	(26)

miR-493	Downregulated	(27)
miRNA-141	Upregulated	(7)
miR-224	Upregulated	(28)
miR-218, miR-425 andmiR-183	218 Down and 425 Up	(29)
miR-486-5p and miR-30a-5p	Downregulated	(30)
miRNA-21 and miRNA-155	Upregulated	(31)
(miR-21high and miR-188high	Upregulated	(32)
Hsa-let-7f-5p, hsa-let-7b-5p	7b-5p Down and 7f-5p Up	(33)
Hsa-miR-30d, hsa-let-7b	30d Down and 7b Up	(34)
miR-148a	Upregulated	(35)
MiR-378	Upregulated	(36)
microRNA-29a acted as a tumor suppressor	Downregulated	(37)
hsa_circRNA_103827 and 000122	122 Down, 827 Up	(38)

Table No.3: Reported MicroRNAs in Lung Cancer in Pleural and Bronchial fluids from 2011 to 2018

Significant MicroRNAs	Expression UP/Down	References
miR-198	Downregulated	(39)
miR-134, miR-185, and miR-22	Downregulated	(40)
miR-17-92 cluster	Upregulated	(12)

Table No.4: Reported MicroRNAs in Lung Cancer in Pleural and Brochial fluids from 2011 to 2018

Authors	Region	Cases/Control	Specimen	References
Han et al. (2013)	South Korea	107/NA	Pleural fluid	**(39)**
Shin et al. (2014)	South Korea	129/NA	Pleural fluid	**(40)**
Pineloet al. (2017)	Spain	27/16	Bronchoalveolar lavage fluid	**(12)**

In pleural and broncho-alveolar lavage fluid, miR-198, miR-185, miR-22 and miR-17-92 cluster were observed dysregulated in which miR-198, miR-134, miR-185 and miR-22 were downregulated in pleural fluid whereas miR-17-92 cluster were upregulated in broncho-alveolar lavage as given in table No.3 and 4.

Various researchers examined the miRs in lung cancer tissues and pleural fluid. The miRs serve have potential promising role as a biomarkers for therapeutic purpose and easily detectable in different specimen of human body in lung cancer as compared to healthy individuals.

Present review suggests that a wide range of miRs detected which could be used for diagnosis of lung cancer. The present review support the idea by using miRs as a biological marker for detection of lung cancer (any type or stage) patients. Most of studies detect panel of miRs rather than single miR.

About 38 miRs were extracted from different reports as a tissue and pleural fluid markers in which mir-183 were upregulated frequently reported by three different researchers in different regions(16, 26, 29). In 2011, Zhu et al. from China reported that mir-183 were over expressed in tissue and sera specimen with a sample of 70 pair lung cancer and control group(16). Similar result of upregulated mir-183 were revealed by Edmond et al. (2014) and Wang.et.al (2015) from USA and China respectively, with a different sample size and detection method(26, 29). Overexpression of mir-96 were reported by Zho et al. and Edmond et al.(26, 29). Upregulated mir-196a was reported from China and Japan by Liu et al. (2012) and Hamamoto et al. (2013) respectively, through qRT-PCR with different sample size(18, 24). Downregulated mir-29 result were noted by Rothschild et al. (2012, USA) and Liu et al. (2018, China) with different sample sized and method of detection [19, 37].

Consistent report shown by Yong et al. (2012, China) and Hamamoto *et al*. [22, 24] that mir-205 are upregulated in lung cancer patient, both use different techniques for miRs detection with a variable sample size.

Contradictory were observed in expression of Hsa-mir-let-7b-5p between reports of two researchers, Fazio *et al*. (2017) from Germany reported upregulated in 18 lung cancer patients with a comparison of 4 control individuals samples though RT-PCR [33] whereas Hosseini *et al.* (2017) from Tehran revealed that let-7b-5p were down-regulated in 24 lung cancer participants as compared to 10 control samples through qRT–PCR [34].

Current review study also shows that no similar miRs were observed in samples, which are found in both pleural fluid and tissues samples. Additionally, also shows that different techniques were use for detection which determined similar upregulation of microRNAs mir-183(16, 26, 29). These studies have no contradictory, although there sample size, study setting and detection techniques are varying.

This study suggests that significant miRs were detected in lung cancer in which some are also reported by others researcher from other regions. These significant dysregulated miRs could be used as diagnostic biomarkers in earlier lung cancer patients as compared to control group.

Clinical implication of seven frequently observed microRNAs in lung cancer tissues

Overexpression of mir-96 were noted in different studies (16, 26) and known onco-miRs, mainly target the transcription factor (for head box O3) through binding with 3'UTR region (41, 42).

The significant upregulation of miRs-183 are reported in various types of cancer including lung cancer(16, 43, 44). The mir-183 is an onco-microRNA, target the phosphatase and tensin homolog (PTEN) and tumor suppressor transcription factor (EGR1) to boost up the migration of tumor cell [45]. Reported data shows that mir-183 is involved in invasion, prognosis and metastasis of tumor to different region of human body. Increased expression of mir-183 act as biomarker in lung cancer in both NSCLC and SCC(46).

The increase expression of mir-196a isdescribed in few studies in lung cancer tissues(18, 24). The mir-196a are involved in the tumor cell migration into tissues and liquefaction of extracellular protein (18) and also activate the signaling of AKT pathway and promote invasion and metastasis process but have no impact on proliferation(47).

Reduced expression of mir-29 were noted in several cancer (including lung cancer) patients as compared to healthy individual due to controlling the signal of cell invasion of lung cancer as well as in other cancers(19, 37). Reported data revealed that there is a negative correlation between mir-29 and ID1 by c-Myc due to overexpression of c-Myc in cells of lung cancer suppressed the level of mir-29(19).

High level of mir-205 were also reported by various research studies in lung cancer(24), not only in lung cancer but also in other cancer as well(48, 49). Additionally, types of lung cancer can be distributed through mir-205 and also regulates the expression of PTEN(50).

The expression of mir-21 were upregulated in lung cancer reported by several studies(31, 34). Moreover, high expression of mir-21 are related with poor prognosis and high incidence of mortality(51). In addition, mir-21 have a role in node metastasis and also targeting the tumor suppressor gene TPM1 and also play a role in cell proliferation, differentiation and apoptosis(52, 53).

Hsa-let-7b-5p is frequently determined in several studies including lung cancer(54-59). According to several reported data, Hsa-let-7b-5p were upregulated in solid tumors in lung cancer patients as compared to control group (26, 34, 54, 60) whereas downregulated were revealed by other researchers in tumor tissue after comparing with non-cancerous tissues (32, 61, 62) which is explained with fact that cancer associated fibroblasts have may affect on the expression of results(62).

CONCLUSION

In conclusion, most consistent reports were noted which shows dysregulations of miRs in lung cancer tissues. There is much excitement and interest that miRs are quicker, less invasive, cost effective and synergistic diagnostic markers for lung cancers. In current study, we identify seven highly significant miRs and consistently dysregulated (Up/Down expression) across 27 different studies. There was variation in number of sample and different detection method. The result of present review clearly demonstrates that lung cancer miRs expression might give some indication about potential significant biomarkers and monitoring tumor dynamics. A diagnostic, prognostic and therapeutic biological marker of lung cancer is ambitious. However, observing different significant miRs markers from 2011-2018 provide important biomarkers as a diagnostic marker. Thus, after observation of common miRs in tumor affect tissue are crucial as new diagnostic options and prognostic markers but still hurdle are there in their sensitivity and specificity considerations. Additionally, it is also required to investigate the contradiction between reports on account of hsa-let-7b with similar instruments and technique with same paired samples of tumor and adjacent non-cancerous tissues. Neglect the other obstruction; we believe that miRs will not be only non-invasive diagnostic and screening test for lung cancer but also a future therapeutic target in modern molecular oncology. The limitation of current review is that lack of sensitivity and specificity of these seven different miRs in lung cancers by using efficient and optimized methods. Furthermore, to improve the efficiency and accuracy of these miRs in lung cancers required combined and selective or individuals investigation. Present finding are required to be confirmed in future by clinical investigation. In current context, we hope present review will stimulate researchers for improvement and clinical management of lung cancers patients. For future it is needed to make a panel of these seven miRs for further validation with the normalization of controls, other biological specimen and optimal panel of miRs.

DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no conflicts of interest in account of authorship and/or publication of this review article.

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CITATION OF THIS ARTICLE

A Muhammad, N Ullah, H U Khan, M J Khan. MicroRNAs in Lung Cancer tissues and Pleural fluids: A Review. Bull. Env. Pharmacol. Life Sci., Vol 8 [9] August 2019: 01-08