MiRNA Molecular Profiles in Human Medical Conditions: Connecting Lung Cancer and Lung Development Phenomena

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REVIEW

MiRNA Molecular Profiles in Human Medical Conditions: Connecting Lung Cancer and Lung Development Phenomena

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Abstract

MiRNAs are endogenous, single stranded ~22-nucleotide non-coding RNAs (ncRNAs) which are transcribed by RNA polymerase II and mediate negative post-transcriptional gene regulation through binding to 3'untranslated regions (UTR), possibly open reading frames (ORFs) or 5'UTRs of target mRNAs. MiRNAs are involved in the normal physiology of eukaryotic cells, so dysregulation may be associated with diseases like cancer, and neurodegenerative, heart and other disorders. Among all cancers, lung cancer, with high incidence and mortality worldwide, is classified into two main groups: non-small cell lung cancer and small cell lung cancer. Recent promising studies suggest that gene expression profiles and miRNA signatures could be a useful step in a noninvasive, low-cost and repeatable screening process of lung cancer. Similarly, every stage of lung development during fetal life is associated with specific miRNAs. Since lung development and lung cancer phenomena share the same physiological, biological and molecular processes like cell proliferation, development and shared mRNA or expression regulation pathways, and according to data adopted from various studies, they may have partially shared miRNA signature. Thus, focusing on lung cancer in relation to lung development in miRNA studies might provide clues for lung cancer diagnosis and prognosis.

Keywords: miRNA - medical conditions - lung cancer - lung development

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Introduction

Definition and history of microRNA (miRNA)

MiRNAs are endogenous, single stranded ~22-nucleotide non-coding RNAs (ncRNAs) which mediate negative post-transcriptional gene regulation through binding to 3'untranslated regions (UTR), possibly open reading frames (ORFs) or 5'UTR of target mRNAs (Ambros, 2004; Bartel, 2004; He and Hannon, 2004; Chen and Rajewsky, 2007; Filipowicz et al., 2008). The sequences of miRNAs are highly conserved among unicellular and multi-cellular eukaryotic organisms, represents that miRNAs have a relatively old and important role in regulatory pathways. By regulating gene expression at the posttranscriptional level, miRNAs are profoundly implicated in almost every aspect of cell physiology and central biological processes such as development, cell proliferation, differentiation, metastasis and apoptosis (Grosshans and Slack, 2002; Esau et al., 2004; Xu et al., 2004; Boehm and Slack, 2005; Wang et al., 2007). About 33% of the human genes are regulated by miRNAs, the most abundant class of human gene regulators (Lai et al., 2003; Mattes et al., 2008). More than a half of miRNA genes are localized in regions of loss-of-heterozygosity, amplification, breakpoints or chromosomal fragile sites (Calin et al., 2004). Discovery of the first short non-coding RNA backs to 1993 when Ambros et al. found that Lin-4 was as a regulator of developmental timing in nematode Caenorhabditis elegans (Lee et al., 1993). Let-7 was the second miRNA which was discovered in 2000. Slack et al. reported that let-7 was a heterochronic gene of C. elegans 21nt RNA controlling L4-to-adult transition of larval development. Unlike lin-4, let-7 sequence is highly conserved across species and, as the first miRNA, it was identified in humans to be involved in developmental timing (Reinhart et al., 2000). Since then, researchers have identified and introduced thousands of miRNAs in humans and other species that are now available in miRNA databases such as miRbase.

miRNA biogenesis pathway and its function

MiRNA genes are transcribed by RNA polymerase II into long primary miRNAs (pri-miRNAs) containing a cap structure at the 5' and polyadenylation at the 3' end. Pri-miRNAs are subsequently cleaved by the nuclear microprocessor complex including RNase III Drosha, DiGeorge syndrome critical region gene 8 (DGCR8) and pasha proteins into a structure of 60-110nt long RNA

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called precursor miRNAs (pre-miRNAs) in a process known as "cropping". Alternatively, pre-miRNAs are derived directly from spliced out host gene introns. These so-called "mirtrons" skip the Drosha processing step and are refolded into the stem-loop typical structure of pre-miRNAs, and then enter the sanctioned pathway. Human pre-miRNAs have a 33bp hairpin stem, a terminal loop, and two single-stranded flanking regions upstream and downstream of the hairpin. Pre-miRNAs are then transported by the exportin-5/Ran GTPase complex into the cytoplasm, for further maturation; however, some miRNAs such as miR-29b are not exported to cytoplasm. RNaseIII Dicer-1 enzyme together with TRBP/PACT proteins, cleave cytoplasmic pre-miRNAs into 17-24nt duplex miRNAs which are disentangled by helicase. Two generated strands are "passenger" strand and "guide" strand, which the first one is degraded and the latter one is incorporated into the RNA-induced silencing complex (RISC) and serves as a functional mature miRNA (Figure 1). Complementarity of 6 to 8 bases ("seed" sequence) at the 5' end of the mature miRNA with targeted mRNA UTR elements is important for miRNA's action. Canonically, the selected guide strand together with AGO1 and AGO2 proteins activates RISC, results in translational repression, degradation and destabilization of the target mRNAs (Lee et al., 2002; Lee et al., 2003; Smalheiser, 2003; Yi et al., 2003; Cai et al., 2004; Lund et al., 2004; Gregory and Shiekhattar, 2005; Siomi and Siomi, 2010). Noteworthy to say, some miRNAs can contain additional cis-acting regulatory motifs that might affect their posttranscriptional behavior. Therefore, any disruption in miRNA processing steps can lead to physiological pathway dysfunction and finally diseases. According to a recent study, p53 by binding to DEAD-box RNA helicase p68 (DDX5) interacts with the Drosha microprocessor complex and regulates the processing of pri-miRNAs into pre-miRNAs. This links tumor suppressor p53 to the miRNA biogenesis pathway representing an explanation for disturbance in the function of p53 and miRNA downregulation/upregulation observed in human cancers (Lu et al., 2005; Suzuki et al., 2009).

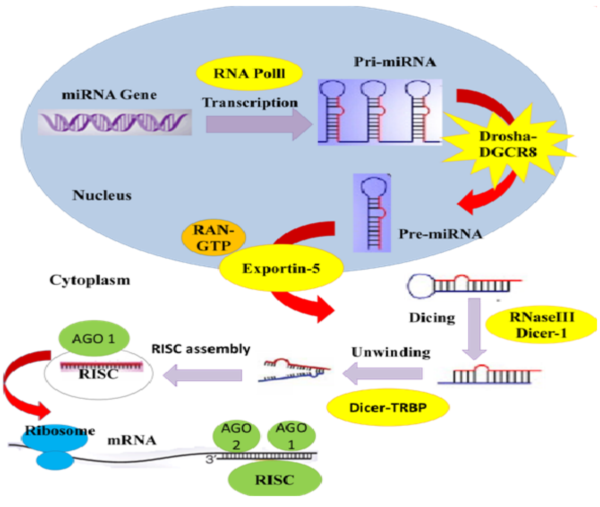

Figure 1. miRNA Biogenesis Mechanism:RNA Polymerase II Produces Pri-miRNAs. Pri-miRNAs are cloven into a structure of 60-110nt long RNA called precursor miRNAs (pre-miRNAs). Pre-miRNAs are then transported by the exportin-5/Ran GTPase complex into the cytoplasm. RNaseIII Dicer-1 enzyme together with TRBP/PACT proteins, cleave cytoplasmic pre-miRNAs into 17-24nt duplex miRNAs. One of the strands is incorporated into the RNA-induced silencing complex (RISC) and serves as a functional mature miRNA which degrades targeted mRNAs (figure 1).

Involvement of miRNAs in medical conditions

Since one single mRNA might be regulated by several miRNAs and one single miRNA might regulate a broad spectrum of mRNAs, investigation of miRNA target genes has been a great issue. Upon this fact, web-based applications and computational algorithms have been established for predicting miRNA targets through seed sequence matching, thermodynamic stability and conservation analysis (Doench and Sharp, 2004; Lim et al., 2005). Concordantly, experimental validation in biological system is needed for target prediction studies. MiRNAs are involved in the normal affairs of eukaryotic cells, so dysregulation of them is associated with diseases (Mraz and Pospisilova, 2012). Hereby, publicly available databases such as miR2Disease have documented evidence-based information for miRNA dysregulation connected human diseases. Besides, expression profiling of miRNAs in various medical conditions has contributed to recognizing miRNAs involved in such diseases which have been comprehensively studied.

miRNAs and cardiovascular diseases

According to miRNA expression profiling studies, expression levels of specific miRNAs is consistent with different kinds of cardiovascular diseases. Furthermore, important role of miRNAs during animal model studies in cardiogenesis, hypertrophic growth response, heart development and cardiac conductance has been revealed (Tatsuguchi et al., 2007; Thum et al., 2007; Zhao et al., 2007). As in Zhao et al. (2007) study, miR-1-1 and miR-1-2 were specifically expressed in cardiomyocytes. In addition to these pioneering studies, miRNA microarray analyzing studies revealed relationship of 12 miRNAs dysregulation during cardiac hypertrophy and heart failure (Zhao et al., 2005; van Rooij et al., 2006).

miRNAs and inherited diseases

Among all studies related to inherited diseases, there are examples of involved miRNAs which are mentioned as follow: MiR-96 mutation is strongly associated with hereditary progressive hearing loss. In one study, hereditary keratoconus was found to be caused by a mutation in the seed region of miR-184. Some authors showed that deletion of the miR-17-92 cluster causes skeletal and growth defects (Mencia et al., 2009; de Pontual et al., 2011; Hughes et al., 2011).

miRNAs and autoimmune diseases

The first inflammatory disease in which miRNAs were studied is a chronic skin disease called psoriasis. Two miRNAs: miR-146 and miR-203 are associated with psoriasis and have specific pattern of expression in patients (Sonkoly et al., 2007; Nestle et al., 2009). Rheumatoid arthritis (RA) characterized by chronic inflammation of synovial tissue was also reported by various studies to be associated with miR-155, miR-146, miR-132, miR16, miR-346 and miR-223 expression change compared with healthy people (Alsaleh et al., 2009; Pauley et al., 2009; Fulci et al., 2010). Sixteen differently expressed miRNAs also were reported to be implicated in another autoimmune disorder, lupus erythematosus (SLE). Some miRNAs are also referred to as regulators of immunological processes such as miR-335 in cognate immune interactions and/or immune synapse formation (Dai et al., 2007; Dai et al., 2009).

miRNAs and neurodegenerative diseases

Although miRNA expression profiling in nervous system is really challenging and difficult because of sampling procedures, a great number of miRNAs appear to be involved at various stages of synaptic development named as miR-132, miR-134, miR-124 and miR-138 (Martino et al., 2009; Schratt, 2009). Since synaptic formation is a process in which neurons are involved and connected to perform their roles in neurological pathways; therefore, it sounds logical that some miRNAs are specifically linked to some neurodegenerative disorders. For instance, miR-9, miR-25b, miR-128 and miR-124a were found to be linked to Alzheimer's disease (Lukiw, 2007; Hugon and Paquet, 2008).

miRNAs and obesity

MiRNAs play critical roles in stem cell differentiation into adipocytes. Unique expression pattern of miR-155, miR-221, let-7 and miR-222 are known to be associated with adipogenesis and obesity. The way for possible obesity treatments on the genetic level is going to be sought in ongoing projects (Zuo et al., 2006; Romao et al., 2011; Skarn et al., 2012).

miRNAs and viral infection

Encoding miRNAs by viruses was not believable until when they found Epstein-Barr virus (EBV) exosomes contain miRNAs. MiRNA involvement in virus infection is exemplified in following study results: The expression of miRNA-146a in human nasopharyngeal carcinoma was elevated by EBV-associated antigen LMP1, probably through the activation of the miRNA-146a promoter (Motsch et al., 2007; Tuddenham et al., 2012; Zhao et al., 2012).

miRNAs and cancers

In 2002 Calin et al. discovered, for the first time, the relationship between a cancer (chronic lymphocytic leukemia) and miRNAs which are deleted from 13q14 region (miR-15and miR-16 coding region) (Calin et al., 2002). To date, distinctive pattern of miRNA expression has been demonstrated in all types of cancer. MiRNAs can act as oncomirs or tumor suppressors in a variety of pathways involved in cancer. Let-7 is an example of tumor suppressors found to be dysregulated in cell culture overexpressing RAS oncogene (Johnson et al., 2005). Also overexpression of miR-17-92 cluster, as oncogene caused to accelerate lymphomagenesis in a mouse B-cell lymphoma model (O'Donnell et al., 2005; Dews et al., 2006). An early-stage colorectal cancer samples were experimented to profile miRNAs, which afterward were proposed for being applied in clinical settings. Similarly, some authors showed that high miR-185 or low miR-133b levels correlated with metastasis in colorectal cancer and high miR-155 (Xu et al., 2013) or low miR-324a level in non-small cell lung carcinoma (NSCLC) could serve as prognostic indicators of such conditions. MiR-205 dysregulation and microRNA-200 family (miR-200a, miR-200b, miR-200c, miR-141 and miR-429) down-regulation has been proved in breast tumors (Gregory et al., 2008; Wu and Mo, 2009; Akcakaya et al., 2011). Accordingly, low miR-127 level was expressed in primary human bladder and prostate tumors in another study (Saito et al., 2006). MicroRNAs deregulation can be caused by several mechanisms including epigenetic mechanisms, deletion, amplification, mutation or dysregulation of transcription factors that target miRNAs. MiRNAs have two opposite roles as promotion and inhibition in every metastatic step process (cell motility, invasion, intravasation, systemic dissemination, extravasation and proliferation at the new site). MiR-10b is an example of positive regulation or promotion in invasion step (Ma et al., 2007). By measuring activity of all genes encoding miRNA, and miRNA signatures or patterns of their expression distinguishing and classification of all types of cancers can be achieved which enable doctors to detect the original cancerous tissue and target a ponderous treatment for cancers (Almeida et al., 2011; Zhang et al., 2012).

Lung cancer and miRNAs

Lung cancer is the leading cause of mortality among all cancers worldwide which is characterized by malignant cell proliferation in lung tissues. This abnormal growth can bring invasion about to other tissues in a process called metastasis. Cancers that start in lung and then enter metastasis process, known as primary lung cancers, are mostly carcinomas derived from epithelial cells. Among two main types of lung cancer, NSCLC reserves greater percentile (80%) than small cell lung carcinoma (SCLC). 80-90% of lung cancers are caused by exposing to tobacco smoke permanently (Sun et al., 2007; Herbst et al., 2008). 92% 5-year survival has been stated to be feasibly attainable by validated, cost-effective screening or diagnosis of lung cancer at early stages. At the time of diagnosis whether (30-40%) NSCLCs or (60%) SCLCs are presented with advanced stages (stage IV). For SCLC, five-year survival is about 5%; in comparison, prognosis for NSCLC would be achieved by complete surgical dissection of stage IA disease. Owing to this rate of survival, investigations for identifying lung cancer, especially NSCLC, at early stage would be precious. Therapeutic strategies designed for targeting specific cellular alterations require precise sub-classification of NSCLCs, which is mainly probable through finding miRNA biomarkers (Zhou et al., 2014) strongly associated with this cancer (Rami-Porta et al., 2009; Fassina et al., 2011; Du and Pertsemlidis, 2012). MiRNAs can be the best candidates to be used as cancer biomarkers because of their high stability. Recent promising studies suggest that gene expression profiles and miRNA signatures could be a useful step in a noninvasive, low-cost and repeatable screening process of lung cancer, and to decide which patients need further screening (Chen et al., 2012; Chen et al., 2013). Recent studies have shown that not only can miRNAs be used for sub-classification and risk stratification of NSCLCs but specific miRNA profiles may also predict prognosis and tumor retrogression. Accumulating evidence states that miRNAs serve as oncogenes or tumor suppressors, and in detailed description as regulators of cellular proliferation and survival, DNA repair, and immune response are grossly dysregulated in human cancers, including NSCLC (Gao et al., 2011; Keller et al., 2011; Lin and Yang, 2011).

Downregulated and/or tumor suppressor miRNAs in lung cancer

In humans, let-7 family is a cluster of miRNAs mapped to various regions of chromosomes and are frequently deleted in lung cancer. Overexpression of let-7 miRNA inhibits cell growth and cell-cycle progression in cell line. Let-7 administered to lung adenocarcinoma patients showed an improvement in diseased people. Furthermore, any reduction in let-7 expression was shown to be highly correlated with NSCLC. Additionally, let-7 miRNAs negatively regulate multiple oncogenes such as RAS, MYC and HMGA2 and cell-cycle progression regulators such as CDC25A, CDK6, and cyclin D2. Collectively, these observations suggest a role for let-7 family miRNAs as tumor suppressors (Johnson et al., 2005; Calin and Croce, 2006; Lee and Dutta, 2007; Kumar et al., 2008). Other examples of miRNAs associated with lung cancer suppression are miRNA-126, miR-874, miR-133b, miR-100 and miR-145 which are downregulated in lung tumor cells. Upregulation of VEGF in one study was inverse to MiR-126 expression, and miR-145 in NSCLC tumor cells showed to act as a tumor suppressor and pro-apoptotic molecule (Bhaskaran et al., 2009; Liu et al., 2012a; Liu et al., 2012b; Kesanakurti et al., 2013). Down-regulation of miR-125a-3p and miR-125a-5p in NSCLCs predicted to be an aggressive clinical course by promoting tumor invasion and lymph node metastasis. Downregulation of miRNA-128b was associated with increased EGFR expression and a consequent survival benefit in patients treated with gefitinib in other studies (Joshi and Kotecha, 2007; Kozuki et al., 2007). In Panel of miRNAs for the early detection of lung adenocarcinoma in sputum miR-21, miR-486, miR-375, and miR-200b showed a significantly different expression in lung adenocarcinoma patients versus normal subjects (Bahl et al., 2008). For instance, miR-SNP haplotypes might allow categorizing lung tumor patients into low, medium, and high-risk groups of disease

Table 1. Downregulated miRNAs in Tumor Tissues of Lung Cancer

No.	miRNA	Fold change	No.	miRNA	Fold change	No.	miRNA	Foldchange
1	hsa-let-7a-1	1.562	41	hsa-mir-148a	4.545	80	hsa-mir-26a-2	1.852
2	hsa-let-7a-3	1.515	42	hsa-mir-151	3.125	81	hsa-mir-28	8.333
3	hsa-let-7b	1.053	43	hsa-mir-152	5	82	hsa-mir-296	1.266
4	hsa-let-7e	50	44	hsa-mir-153-1	4.762	83	hsa-mir-29b-1	33.333
5	hsa-let-7f-2	2.222	45	hsa-mir-153-2	4.762	84	hsa-mir-29b-2	33.333
6	hsa-let-7g	1.205	46	hsa-mir-154	5.882	85	hsa-mir-302a	5.556
7	hsa-let-7i	1.053	47	hsa-mir-183	3.571	86	hsa-mir-302b	3.448
8	hsa-mir-1-1	2	48	hsa-mir-184	1.163	87	hsa-mir-302c	1.887
9	hsa-mir-1-2	1.449	49	hsa-mir-187	4.762	88	hsa-mir-302d	2.174
10	hsa-mir-101-1	25	50	hsa-mir-188	2.5	89	hsa-mir-30d	4
11	hsa-mir-101-2	2.632	51	hsa-mir-191	16.667	90	hsa-mir-32	3.03
12	hsa-mir-105-1	1.724	52	hsa-mir-193a	1.538	91	hsa-mir-320a	1.205
13	hsa-mir-105-2	1.724	53	hsa-mir-194-1	6.667	92	hsa-mir-325	8.333
14	hsa-mir-106a	5.556	54	hsa-mir-194-2	6.667	93	hsa-mir-326	14.286
15	hsa-mir-122	6.25	55	hsa-mir-196a-2	1.163	94	hsa-mir-335	33.333
16	hsa-mir-124-1	4.762	56	hsa-mir-199a-2	1.449	95	hsa-mir-33a	16.667
17	hsa-mir-124-2	4.762	57	hsa-mir-19b-2	50	96	hsa-mir-342	1.042
18	hsa-mir-124-3	4.762	58	hsa-mir-200b	10	97	hsa-mir-34b	3.571
19	hsa-mir-125b-2	4.167	59	hsa-mir-200c	4.545	98	hsa-mir-361	1.667
20	hsa-mir-126	6.667	60	hsa-mir-203	14.286	99	hsa-mir-367	14.286
21	hsa-mir-128-2	6.25	61	hsa-mir-205	14.286	100	hsa-mir-370	1.471
22	hsa-mir-130b	1.667	62	hsa-mir-206	3.333	101	hsa-mir-372	33.333
23	hsa-mir-132	9.091	63	hsa-mir-208a	7.692	102	hsa-mir-373	1.786
24	hsa-mir-135a-1	16.667	64	hsa-mir-20a	3.571	103	hsa-mir-374a	4
25	hsa-mir-135a-2	16.667	65	hsa-mir-215	1.471	104	hsa-mir-375	5.556
26	hsa-mir-135b	2.5	66	hsa-mir-216a	1.471	105	hsa-mir-377	3.571
27	hsa-mir-136	10	67	hsa-mir-217	100	106	hsa-mir-378	7.143
28	hsa-mir-137	8.333	68	hsa-mir-218-1	1.471	107	hsa-mir-379	2.041
29	hsa-mir-138-1	25	69	hsa-mir-218-2	1.471	108	hsa-mir-380	4.545
30	hsa-mir-138-2	25	70	hsa-mir-219-1	5.556	109	hsa-mir-381	16.667
31	hsa-mir-141	7.692	71	hsa-mir-219-2	5.556	110	hsa-mir-382	10
32	hsa-mir-143	1.852	72	hsa-mir-220a	1.111	111	hsa-mir-383	5
33	hsa-mir-144	25	73	hsa-mir-222	1.149	112	hsa-mir-384	20
34	hsa-mir-146a	5.882	74	hsa-mir-223	7.692	113	hsa-mir-423	1.266
35	hsa-mir-147	4.762	75	hsa-mir-26a-1	1.852	114	hsa-mir-424	2.083
36	hsa-mir-9-3	7.692	76	hsa-mir-425	1.961			
37	hsa-mir-92a-1	5.882	77	hsa-mir-7-1	4.167			
38	hsa-mir-92a-2	1.923	78	hsa-mir-7-2	5.882			
39	hsa-mir-95	100	79	hsa-mir-7-3	10			
40	hsa-mir-99a	2.941						

with respect to determinate clinical aspects, such as cancer progression, chance of survival, and response to therapies (Hu et al., 2011; He et al., 2014). Expression profiling studies of miRNAs in lung cancer have been investigated since two decades ago, and many of miRNAs have been confirmed during various investigations which are shown in table below (Supplemental Data, Table 1) (Guan et al., 2012; Markou et al., 2013).

Upregulated and/or oncogene miRNAs in lung cancer

MiR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, miR 92-1 and miR-31 are oncogenes, because they cooperate with c-Myc to accelerate tumor development and neovascularization (Guo et al., 2007; Liu et al., 2010). In accordance with two studies, upregulation of miR-137, miR-372, miR-182, miR-486, miR-30d, miR-1, miR-499, miR-221, and let-7a are correlated with disease-free survival in 122 NSCLC patients (Yu et al., 2008; Hu et al., 2010). MiR-31, miR-212, miR-196a and miR-135b are other examples of miRNAs with oncogenic properties in lung cancer (Liu et al., 2010; Li et al., 2012; Liu et al., 2012c; Lin et al., 2013). LATS2 and PPP2R2A are tumor suppressors which are repressed by miR-31 as it was shown by Liu et al. representing that miR-31 is an oncomir. This miR-31/ LATS2/PPP2R2A also was reported to be involved in a pathway constitutes a new growth regulator in lung cancer (Liu et al., 2010). Accordingly using microarray and real-time PCR expression assays plenty of lung cancer miRNA profiles have been verified in related studies which are shown in table below (Supplemental Data, Table 2).

Lung development and miRNAs

There are considerable differences in timing and stages of lung growth in human and animals, but generally development of this system encompasses 5steps. The first four stages occur during gestation, and the final stage starts at 24th week and continues through early childhood (Bhaskaran et al., 2009; Mujahid et al., 2013).

Step 1- Embryonic stage (3-7 wk- E9-11.5): Formation of trachea and main stem bronchi, the segments of the individual pulmonary lobes that is raised at the end of this period. Step 2- Pseudo glandular stage (5-17 wk-E11.5-16.5): Proliferation of bronchial branches, primitive differentiation of airway epithelium. Step 3-Canalicular stage (16-26wk -E16.5-17.5): the airway branching pattern is completed and the prospective gas-exchange region starts to develop, a large part of the amniotic fluid is produced by the lung epithelium. Step 4- Saccular stage (24-38 wk- E 17.5-P5): Alveolar duct and air sacs is formed, and the last generation of air spaces in the respiratory part of the bronchial tree is born. Step 5-Alveolar stage (38 wk to maturity- P5-30): The alveoli form from the terminal endings of the alveolar sacculi and with time increase, their diameter increases in number of terminal saccules, alveolar ducts, and alveoli (Joshi and Kotecha, 2007). Since accessing to lung tissues during its development in embryonic stages is highly invasive and

Table 2. Upregulated miRNAs in Tumor Tissues Of Lung Cancer

No.	miRNA	Fold change	No.	miRNA	Fold change	No.	miRNA	Foldchange
1	hsa-let-7a-2	21.77	37	hsa-mir-181c	2.8	73	hsa-mir-301a	2.62
2	hsa-let-7d	1.72	38	hsa-mir-182	11.72	74	hsa-mir-30a	1.77
3	hsa-let-7f-1	1.73	39	hsa-mir-185	9.83	75	hsa-mir-30b	2.48
4	hsa-mir-100	27.96	40	hsa-mir-186	4.89	76	hsa-mir-30c-1	2.11
5	hsa-mir-103-1	19.34	41	hsa-mir-18a	13.26	77	hsa-mir-30c-2	2.11
6	hsa-mir-103-2	19.34	42	hsa-mir-192	1.37	78	hsa-mir-30e	1.77
7	hsa-mir-106b	3.69	43	hsa-mir-195	21.63	79	hsa-mir-31	11.45
8	hsa-mir-107	28.28	44	hsa-mir-196a-1	1.09	80	hsa-mir-328	4.96
9	hsa-mir-10a	1.01	45	hsa-mir-196b	6.34	81	hsa-mir-330	1.4
10	hsa-mir-10b	1.01	46	hsa-mir-197	22.76	82	hsa-mir-331	1.09
11	hsa-mir-125a	2.87	47	hsa-mir-198	6.86	83	hsa-mir-337	1.62
12	hsa-mir-125b-1	3.26	48	hsa-mir-199a-1	11.58	84	hsa-mir-338	2.11
13	hsa-mir-127	14.39	49	hsa-mir-199b	8.97	85	hsa-mir-339	4.02
14	hsa-mir-128-1	1.44	50	hsa-mir-19a	2.88	86	hsa-mir-340	1.03
15	hsa-mir-129-2	12.36	51	hsa-mir-19b-1	1.87	87	hsa-mir-345	5.31
16	hsa-mir-130a	14.56	52	hsa-mir-200a	224.57	88	hsa-mir-346	9.11
17	hsa-mir-133a-1	1.26	53	hsa-mir-204	4.16	89	hsa-mir-34a	1.15
18	hsa-mir-133a-2	1.26	54	hsa-mir-21	221.66	90	hsa-mir-365-2	1.38
19	hsa-mir-133b	4.07	55	hsa-mir-210	46.37	91	hsa-mir-371	3.55
20	hsa-mir-134	6.38	56	hsa-mir-211	11.57	92	hsa-mir-376a-1	1.14
21	hsa-mir-139	1.37	57	hsa-mir-212	2.04	93	hsa-mir-422a	1.91
22	hsa-mir-142	5.71	58	hsa-mir-214	5.37	94	hsa-mir-9-1	4.03
23	hsa-mir-145	1.13	59	hsa-mir-22	4.09	95	hsa-mir-9-2	5.68
24	hsa-mir-148b	1.29	60	hsa-mir-221	1.31	96	hsa-mir-93	1.36
25	hsa-mir-149	4.25	61	hsa-mir-224	2.03	97	hsa-mir-96	58.9
26	hsa-mir-150	1.27	62	hsa-mir-23a	1.36	98	hsa-mir-98	18.83
27	hsa-mir-155	1.33	63	hsa-mir-23b	4.1	99	hsa-mir-99b	9.27
28	hsa-mir-15a	1.49	64	hsa-mir-24-1	31.53	100	hsa-mir-301a	2.62
29	hsa-mir-15b	5.93	65	hsa-mir-24-2	31.53	101	hsa-mir-30a	1.77
30	hsa-mir-16-1	4.63	66	hsa-mir-25	1.3	102	hsa-mir-30b	2.48
31	hsa-mir-16-2	3.39	67	hsa-mir-26b	4.4	103	hsa-mir-30c-1	2.11
32	hsa-mir-17	7.88	68	hsa-mir-27a	3.62	104	hsa-mir-30c-2	2.11
33	hsa-mir-181a-1	1.58	69	hsa-mir-27b	3.62	105	hsa-mir-30e	1.77
34	hsa-mir-181a-2	2.8	70	hsa-mir-299	3.23	106	hsa-mir-31	11.45
35	hsa-mir-181b-1	1.66	71	hsa-mir-29a	2.22	107	hsa-mir-328	4.96
36	hsa-mir-181b-2	1.66	72	hsa-mir-29c	2.22	108	hsa-mir-330	1.4

Table 3. miRNA Expression in Lung Development [76, 94-96]

miRNA	Human	Mouse	Expression –stage	References	miRNA	Human	Mouse	Expression –stage	References
Cluster miRNA 17-92(mir-17, 18a, 19a, 19b-1, 20a, and 92-1)		✓	Low expression - E11.5-17.5/ E16-AD	Lu et al. Bhaskaran et al. Tang et al.	miR-21		✓	High expression-(E11.5-17.5) - foetal lung	Lu et al. Tang et al.
Cluster miRNA miR-106a(mir-20b, 90a-2 and 106a)		✓	Low expression - E11.5-17.5	Lu et al.	miR-195		✓	High expression-E16-AD -(1d-60d)	Bhaskaran et al. Williams et al.
miR-30families (miR-30a, miR-30d, miR-30e, miR-30b, miR-30c, miR-30e)	✓	✓	High expression - Adulthood stage(E11.5-17.5) -(1d-60d)	Dong et al. Lu et al. Williams et al.	miR-298		✓	Low expression-E16-AD	Bhaskaran et al.
miR-24 families (miR-24, miR-24-2)		✓	High expression - Adulthood stage	Dong et al.	miR-341		✓	Low expression-E16-AD	Bhaskaran et al.
miR-26 families (miR-26a, miR-26b	✓	✓	High expression - Adulthood stage	Dong et al. Williams et al. Tang et al.	miR-130b		✓	Low expression-E16-AD/ (E11.5-17.5)	Bhaskaran et al. Lu et al.
miR-29 families (miR-29a, miR-29c)	✓	✓	High expression - Adulthood stage-(1d-60d)	Dong et al. Williams et al.	miR-214		✓	Low expression-E16-AD/ (E11.5-17.5)/(1d-60d)	Bhaskaran et al. Lu et al. Williams et al.
miR- 34 families (miR-34b-3p, miR-34c)	✓	✓	High expression - Adulthood stage-(1d-60d)	Dong et al. Williams et al.	miR-106b		✓	Low expression-E16-AD/ (E11.5-17.5)	Bhaskaran et al. Lu et al.
miR-20 families (miR-20a, miR-20b)		✓	High expression - early stages/down (E11.5-17.5)	Dong et al. Lu et al.	miR-93		✓	Low expression-E16-AD/ (E11.5-17.5)	Bhaskaran et al. Lu et al.
miR-21	✓	✓	High expression- Adulthood stage	Tang et al. Williams et al.	miR-290		✓	Low expression-E16-AD	Bhaskaran et al.
let 7		✓	High expression -E11.5-17.5	Lu et al. Tang et al.	miR-23a		✓	High expression-E16-AD-down -(E11.5-17.5)-up(1d-60d)	Bhaskaran et al. Lu et al. Williams et al.
miR-8		✓	High expression -E11.5-17.5	Lu et al.	miR-22		✓	High expression-E16-AD	Bhaskaran et al.
miR-127		✓	High expression- early stages-E21	Bhaskara et al.	miR-351		✓	High expression-E19(E11.5-17.5)	Bhaskaran et al. Lu et al
miR-210		✓	High expression	Bhaskaran et al.	miR-15a-b		✓	High expression-E16-AD -(E11.5-17.5)	Lu et al.
miR-19b		✓	High expression- Low expression	Bhaskaran et al. Lu et al.	let-7b	✓	✓	High expression-E16-AD) (1d-60d)	Bhaskaran et al. Lu et al.
miR-29a		✓	High expression-E16-AD	Bhaskaran et al.					

kind of impossible, and miRNA profiles of every stage should be separately studied due to their huge distinctive properties, miRNA expression studies are confined to assimilated cell line and animal trials. Several miRNA has been detected in mouse and human lung development. However in human, expression investigations are few in number and ongoing. According to several studies, miRNAs are assumed to be multifunctional molecules in lung development. Many authors have stated that the expression of miRNAs is distinctly dissimilar in the early stages of lung organogenesis to adulthood stage. Therefore, we classified miRNA signatures in each stage to make the whole lung development expression profiling conceivable which is shown in table below (supplemental data, Table 3 (Lu et al., 2008; Bhaskaran et al., 2009; Dong et al., 2010; Tang et al., 2011; Mujahid et al., 2013)).

Shared and non-shared miRNAs between lung cancer and lung development phenomena

Since lung development and lung cancer phenomena share some similar physiological, biological and molecular processes like cell proliferation, development, having in-common mRNA signatures and etc, and according to data adopted from various studies, they may have partially shared miRNA signature (as shown in Table 1 below). Therefore, it helps scientists find the functional pathway of a great deal of miRNAs involved in abovementioned procedures. In this regard, we may allude to some predictions. For example, PI3K/AKT pathway is activated in both developmental processes and cancers. Overexpression of miR-21 can lead to cancer through binding to 3'UTR elements and silencing of PTEN, which subsequently PI3K/AKT pathway is activated (Bueno et al., 2008). So it sounds logical to observe miR-21 up-regulated in both lung development and lung cancer phenomena as indicated in Table 1. Another miRNA, miR-20a, which is down-regulated in both lung cancer and lung development as shown in Table 1, is correlated with conditions like NSCLC and SCLC and pathways like TGF-beta, MAPK and Wnt signaling pathways and also cell cycle that are principles of cell proliferation which is a process shared in both lung development and lung cancer.

Conclusions

As the day investigators discovered and introduced miRNAs for the first time as a key regulator of gene expression, a variety range of experiments throughout the world have been conducted for determination of miRNAs and their role in cell biological affairs. MiRNA expression profiling studies in parallel with functional genome studies are going to reveal the precise function of miRNAs in body which subsequently will probably explain molecular pathways tied in ambiguity during past decades. Dysregulation of miRNAs has been tangled with different kinds of complications in human medical conditions especially genetic disorders. Studying lung cancer particularly NSCLC as a medical condition through miRNA expression profiling would be worthy owing to early stage diagnosis and prognosis and also high rate of survival that had been possible by means of developing treatment strategies. Reporting series of miRNAs as biomarkers in blood and urine of lung cancer patients for molecular diagnostic testing paves the way to noninvasive diagnosis and classification of this cancer into specific subgroups. Besides, knowing procedures and different stages of lung development and connecting it with lung cancer phenomena through miRNA profiles gives us the point of view that shared miRNAs could be served as the possible linkage between two phenomena processes like cell proliferation and eventually bring in novel strategies for tracing such cancer causes. Consequently, early stage diagnosis would be the principal results of investigations in this field of study.

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