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MicroRNAs – important molecules in lung cancer research

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MicroRNAs (miRNA) are important regulators of gene expression. They are involved in many physiological processes ensuring the cellular homeostasis of human cells. Alterations of the miRNA expression have increasingly been associated with pathophysiologic changes of cancer cells making miRNAs currently to one of the most analyzed molecules in cancer research. Here, we provide an overview of miRNAs in lung cancer. Specifically, we address biological functions of miRNAs in lung cancer cells, miRNA signatures generated from tumor tissue and from patients' body fluids, the potential of miRNAs as diagnostic and prognostic biomarker for lung cancer, and its role as therapeutic target.

Keywords: microRNA, lung cancer, body fluids, blood, biomarker, diagnosis, prognosis, therapy

INTRODUCTION

Besides housekeeping genes, the expression of all other genes is mostly regulated through a complex mechanism that enables a cell type specific and time specific expression. Regulations can occur during each step of gene expression, e.g., during chromatin remodeling, transcription and translation, RNA transport, or on the post-transcriptional level. The main gene expression regulators are proteins or enzymes, e.g., histones, transcription factors, and polymerases. Gene expression can also be regulated by antisense or sense nucleic acids (Helene and Toulme, 1990). MicroRNAs (miRNAs) are a highly conserved family of small RNAs (17–22 nt) that regulate the expression of their target genes usually on the post-transcriptional level by binding to complementary sequences on target messenger RNA transcripts (mRNAs) mostly resulting in gene silencing. Since the first description of miRNAs in 1993 by Victor Ambros, Rosalind Lee, and Rhonda Feinbaum in *C. elegans* (Lee et al., 1993) more than 1500 different human miRNAs (see miRBase V18, http://www.mirbase.org) have already been identified. As each miRNA can regulate hundreds of target genes, it is assumed that the majority of the 20,000–25,000 human genes may be regulated by specific miRNAs (van Kouwenhove et al., 2011). Silencing of the target genes is obviously the main regulation mechanism – either by translational repression or by mRNA degradation. Perfect matching of the miRNA to the 3′ UTR of its target mRNA results in direct mRNA degradation whereas imperfect matching – with nucleotides 2–7 of the miRNA (called "seed region") still perfectly complementary – leads to translational repression. Bartel and colleagues analyzed the relative contribution of these two outcomes and found that degradation of the mRNA by miRNAs is with more than 80% of cases the predominant reason for a reduced protein output (Guo et al., 2010). Recently, miRNAs were also shown to up-regulate target gene expression either directly through binding to the target mRNA (Vasudevan et al., 2007) or indirectly through repressing nonsense-mediated RNA decay (Bruno et al., 2011). According to their function miRNAs play an essential role in cellular processes as development, proliferation, and apoptosis ensuring the cellular homeostasis of healthy human cells. An alteration of this cellular homeostasis through aberrant expression of miRNAs likely contributes to many human pathologies including cancer. Calin et al. (2002) revealed for the first time a possible correlation between miRNA deregulation and cancer. Subsequently, a multitude of studies about miRNA expression changes and cancer has been reported.

Lung cancer is worldwide the leading cause of cancer related deaths. The 5-year overall survival rate strongly correlates with the time of diagnosis and varies between 60 and 80% in clinical stage I to only 1% in clinical stage IV. Unfortunately, lung cancer is mostly diagnosed in late stages. Currently, no appropriate biomarker exists to detect lung cancer at early stages. Takamizawa et al. (2004) were the first to relate miRNA expression to lung cancer. Since then the number of publications dealing with the relation between miRNA expression and lung cancer has raised to above 400.

In this review we place emphasis on the current status of miRNA research in lung cancer. Specifically, we focus on current findings on the molecular role of miRNAs in lung cancer development and progression. In addition, we address the potential of miRNA research for tumor diagnosis and therapy.

DETECTION OF miRNAs IN HUMAN SAMPLES

Most of the miRNA expression data have been generated by the analysis of tissue samples with the main focus on cancer tissue. The data collected from tissue samples may provide the best insights into the involvement of miRNAs in a disease state. As miRNAs are markedly stable against degradation, stored formalin-fixed paraffin embedded (FFPE) tissue can be used for miRNA isolation (Liu

and Xu, 2011). Lu et al. (2005) showed that tissue miRNA expression profiles are highly cell type specific and that they reflect the developmental lineage and the differentiation state. MiRNA expression data derived from 40 different tissue samples from healthy individuals revealed both a group of universally expressed miRNAs and groups of tissue specific expressed miRNAs (Liang et al., 2007). Besides tissues, sources for miRNAs can be body fluids such as whole blood, serum, plasma, urine, cerebrospinal fluid (CSF), and – especially in the case of lung cancer research – saliva, sputum, or bronchoalveolar lavage (BAL) (Weber et al., 2010; Tzimagiorgis et al., 2011). MiRNA profiles of body fluids are useful for the analysis of disease states especially when the disease does not originate from one distinct type of cell and when the tissue is not readily accessible, e.g., in neurological disorders (e.g., Schizophrenia, Lai et al., 2011; Alzheimer's Disease, Schipper et al., 2007), in heart failure (Voellenkle et al., 2010; Meder et al., 2011), in autoimmune diseases (e.g., Lupus, Wang et al., 2011), and in respiratory tract diseases (e.g., COPD, Pottelberge et al., 2011). In general, miRNA profiles of body fluids, including urine (Hanke et al., 2010), serum (Mitchell et al., 2008; Otaegui et al., 2009), saliva (Park et al., 2009), sputum (Xing et al., 2010), CSF (Baraniskin et al., 2011) have been discussed as future non-invasive biomarkers. How miRNAs enter the body fluids is still a largely unsolved question. One possibility is that cancer cells without metastatic potential enter the blood stream and release their cell content including miRNAs after passing through a suicide program (Mehes et al., 2001). Alternatively, miRNAs packed in microvesicles or exosomes are actively released in the bloodstream (Hunter et al., 2008; Rabinowits et al., 2009). Notably, miRNAs measured in body fluids frequently reflect different cell types. For example, urine of a bladder cancer patient contains apoptotic or necrotic cells, non-malignant exfoliated urothelial cells, and leukocytes besides tumor cells (Hanke et al., 2010), all of which may contribute to the miRNA expression profile. Saliva contains blood cells, microorganisms, and apoptotic or detached living epithelial cells. Cell-free nucleic acids actively released by cancer and epithelial cells or inactively by apoptotic cells and micro-wounds have also been found in saliva (Park et al., 2006). Likewise, different cell types contribute to miRNA profiles in sputum (Thunnissen, 2003; Xie et al., 2010; Yu et al., 2010), BAL (Ahrendt et al., 1999; Schmidt et al., 2005), and CSF (Karlsson et al., 2001; Reiber and Peter, 2001).

In conclusion, the measurement of miRNAs in body fluid has high potential for future non-invasive diagnostic tests especially for cancer. There are, however, various hurdles to be overcome to turn a miRNA signature into a diagnostic tool. Among others, the amount of specific miRNAs may be limited in certain body fluids, the availability of body fluid may also be limited, standardized protocols have not yet been established for the isolation and analysis of RNA from body fluids, and detection methods have to be optimized. As for the latter, microarray experiments are both cost-intensive and time-consuming while qRT-PCR lacks reliable endogenous controls for body fluids.

THE MOLECULAR BIOLOGY OF miRNAs IN LUNG CANCER

The first aberrantly expressed miRNA in lung cancer was identified in 2004 (Takamizawa et al., 2004). By analyzing 143 potentially curative resected lung cancer samples Takamizawa et al. (2004) showed that a reduced let-7 expression is correlated with a shorter post-operative survival. They confirmed their results by introducing let-7 into the adenocarcinoma cell line A549. The observed overexpression resulted in growth inhibition of the cells. These findings laid the basis for further studies on the molecular mechanisms of the tumor suppressor function of let-7. The 3′ UTR of HRAS, KRAS, and NRAS that are members of the RAS GTPase family, contain multiple putative let-7 binding sites. The expression of let-7 in lung cancer was inversely correlated to RAS expression. On the basis of these results Johnson et al. (2005) concluded that let-7 is a negative regulator of the oncogene RAS. Microarray analysis revealed additional genes whose expressions were altered in the presence of excess let-7 (Johnson et al., 2007). These genes include key cell cycle proto-oncogenes such as CDC25a, CDK16, and cyclin D that are involved in the G1/S transition. These findings gave further support to the assumption that let-7 functions as tumor suppressor miRNA. Recently, let-7 was shown to target BCL-2, thereby inhibiting the growth of A549 cells (Xiong et al., 2011). As BCL-2 is a proto-oncogene involved in regulation of apoptosis, a negative regulation through let-7 may result in growth suppression and apoptosis induction of A549 cells. Esquela-Kerscher et al. (2008) confirmed that let-7 reduces *in vivo* tumor growth of lung cancer cell xenografts in immunodeficient mice.

Hayashita et al. (2005) found an overexpressed intronic miRNA cluster (miR-17-92) encompassing seven different miRNAs namely hsa-miR-17-5p, hsa-miR-17-3p, hsa-miR-18a, hsa-miR-19a, hsa-miR-19b-1, hsa-miR-20a, and hsa-miR-92 in the amplified chromosomal region 13q31.3 in lung cancer, mostly in small cell lung cancer. This polycistronic miRNA cluster was first described by He et al. (2005) in B-cell lymphomas. Antisense oligonucleotides against mir-17-5p and miR-20a were shown to induce apoptosis in mir-17-92 overexpressing lung cancer cells (Matsubara et al., 2007). Recently, Kanzaki et al. (2011) were able to identify several direct targets of the miR-17-92 oncogene. A summary of the various roles of the miR-17-92 cluster was given by Joshua T. Mendell in Cell (Mendell, 2008).

Besides hsa-let-7 and the miRNAs of the miR-17-92 cluster, there are numerous reports on other miRNAs that are deregulated in lung cancer tissue, e.g., hsa-miR-21 whose overexpression was suggested to be an independent negative prognostic factor for the overall survival in NSCLC patients (Markou et al., 2008; Gao et al., 2010). Hsa-miR-21 targets tumor suppressor genes such as programmed cell death 4 (Pdcd4; Lu et al., 2008) and PTEN (Zhang et al., 2010). There is evidence that the expression of miRNA-21 is up regulated by epidermal growth factor receptor (EGFR)-signaling in lung cancer (Seike et al., 2009). In 15% of all lung cancer patients, mostly never-smokers, EGFR contained a mutation resulting in constitutive activation of tyrosine kinase (TK), which in turn leaded to tumor progression (da Cunha Santos et al., 2011). The inhibition of the EGFR signaling by a tyrosine kinase inhibitor (TKI) resulted in a reduced expression of miR-21 (Seike et al., 2009). But, since miR-21 is also deregulated in several other cancer types, it seems to be a general oncogenic miRNA without tissue specificity (Ciafre et al., 2005; Volinia et al., 2006; Iorio et al., 2007; Meng et al., 2007).

IMPACT OF miRNA RESEARCH ON CLINICAL ONCOLOGY

The 5-year survival of lung cancer patients is 15% for all stages combined. Early detection of lung cancer in high-risk patients is likely to improve the prognosis. Currently, less than 20% of lung cancer patients are diagnosed with a locally confined tumor (Jemal et al., 2009). This low detection rate calls for the identification of new reliable biomarkers to allow non-invasive early detection of locally confined lung cancers. The markers should also contribute to the distinction between benign and malignant lesions.

MicroRNAs play an essential role in lung development (Tomankova et al., 2010). Due to the different expression pattern in healthy lung tissue compared to lung cancer tissue it seemed legitimate to assume that aberrant miRNA expression may be involved in the onset of lung cancer (Mascaux et al., 2009; Megiorni et al., 2011). By microarray analyses of the miRNA expression in 104 pairs of primary lung cancers and corresponding non-cancerous lung tissues Yanaihara et al. (2006) identified a specific miRNA profile, encompassing 43 differentially expressed miRNAs. Volinia et al. (2006) performed a large-scale analysis of the miRNA profiles of 540 samples, encompassing 363 samples from patients with six different types of solid tumors including lung cancer and 177 normal tissue samples. They identified a cancer miRNA signature with mostly overexpressed miRNAs. Besides the identification of cancer type specific miRNA signatures, research is also aiming at the identification of specific miRNAs that are suited to differentiate between histological lung cancer subclasses. As treatment depends on the histological subtype, such miRNAs are likely to be useful for decision-making in clinical treatment. Lebanony et al. (2009) were able to provide a highly accurate subclassification of NSCLC patients. They identified miR-205 as suitable marker for squamous cell lung carcinoma by comparing the miRNA expression pattern between 122 adenocarcinoma and squamous NSCLC samples (Lebanony et al., 2009). MiRNA signatures also appeared suitable to distinguish SCLC cells from NCLC cells (Du et al., 2010). Vosa et al. (2011) provided evidence for miR-374 as a potential marker for early stage NSCLC. Recently, different groups were able to identify miRNAs that differentiated NSCLC patients with brain metastases from patients without brain metastases (Arora et al., 2011; Nasser et al., 2011). Biomarkers that allow identification of NSCLC patients with increased risk for brain metastases will be of great value for the decision-making in preventive radiation treatment.

As miRNAs are very stable not only in tissue but also in body fluids, they offer themselves as potential biomarker for non-invasive early detection of lung cancer. Especially, for lung cancer the poor survival time and the high relapse rates after surgery call for new methods to detect the disease at early stage. MiRNA expression patterns have also the potential to be a useful prognostic tool. In addition, there is growing interest to use miRNAs as therapeutic agent. Especially the increasing knowledge about the role of miRNAs as tumor suppressors or activators of oncogenes, will help to develop novel miRNA-based therapeutic approaches. **Figure 1** provides an overview about potential different clinical applications of miRNAs in oncology. **Figure 2** gives an overview of the potential time points for the application of lung cancer specific miRNAs. **Table A1** in Appendix provides information on miRNAs associated with lung cancer.

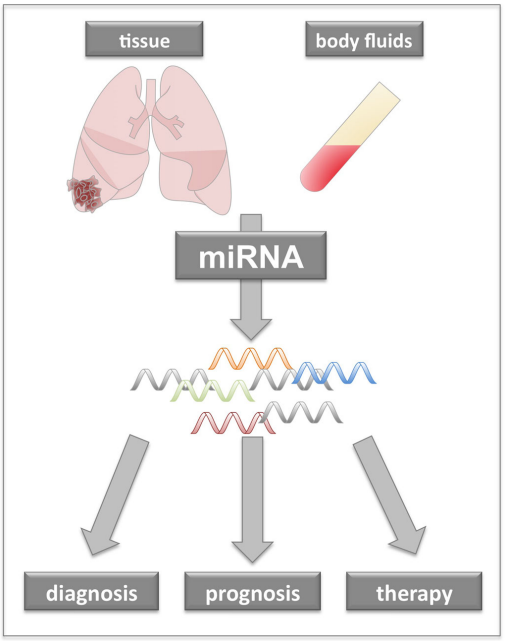

FIGURE 1 | The impact of miRNA research on clinical oncology. Alterations in miRNA expression are associated with pathophysiological changes in cancer cells. As miRNA signatures from cancer tissue or patients' body fluids differ from those of healthy individuals miRNA signatures may likely to contribute to improved early diagnosis or patients' prognosis. Through altered expression single miRNAs may act as oncogene or they may loose their tumor suppressor properties. Those miRNAs could be utilized for anti-cancer therapy.

miRNAs AS POTENTIAL DIAGNOSTIC BIOMARKER FOR LUNG CANCER

It is well known that the onset of cancer impacts the immune system leading to changes in the gene expression of blood cells (Pardoll, 2003; Kossenkov et al., 2011). Jeong et al. (2011) showed that the expression of let-7a is reduced not only in lung cancer tissue, but also in blood of lung cancer patients compared to healthy individuals. In our recent studies, we were able to separate blood samples of lung cancer patients from blood samples of healthy individuals by miRNA signatures with a specificity of 98.1% and a sensitivity of 92.5% (Keller et al., 2009). In addition we reported miRNA signatures that differentiated blood samples of lung cancer patients from blood samples of patients with non-malignant chronic obstructive pulmonary disease with 89.2% specificity, and 91.7% sensitivity (Leidinger et al., 2011). Recently, we showed in a multicenter study that different types of cancer or non-cancer diseases could be differentiated by blood-borne miRNA profiles (Keller et al., 2011a).

As above mentioned, miRNAs are also present in other body fluids. Yu et al. (2010) showed that miRNAs were stably present in sputum. They were able to differentiate lung adenocarcinoma patients from healthy individuals by using a panel of four sputum miRNAs namely miR-486, miR-21, miR-200b, and miR-375, with high sensitivity (80.6%) and specificity (91.7%; Yu et al., 2010). The same group identified three sputum miRNAs, namely miR-205, miR-210, and miR-708 that distinguished squamous cell lung

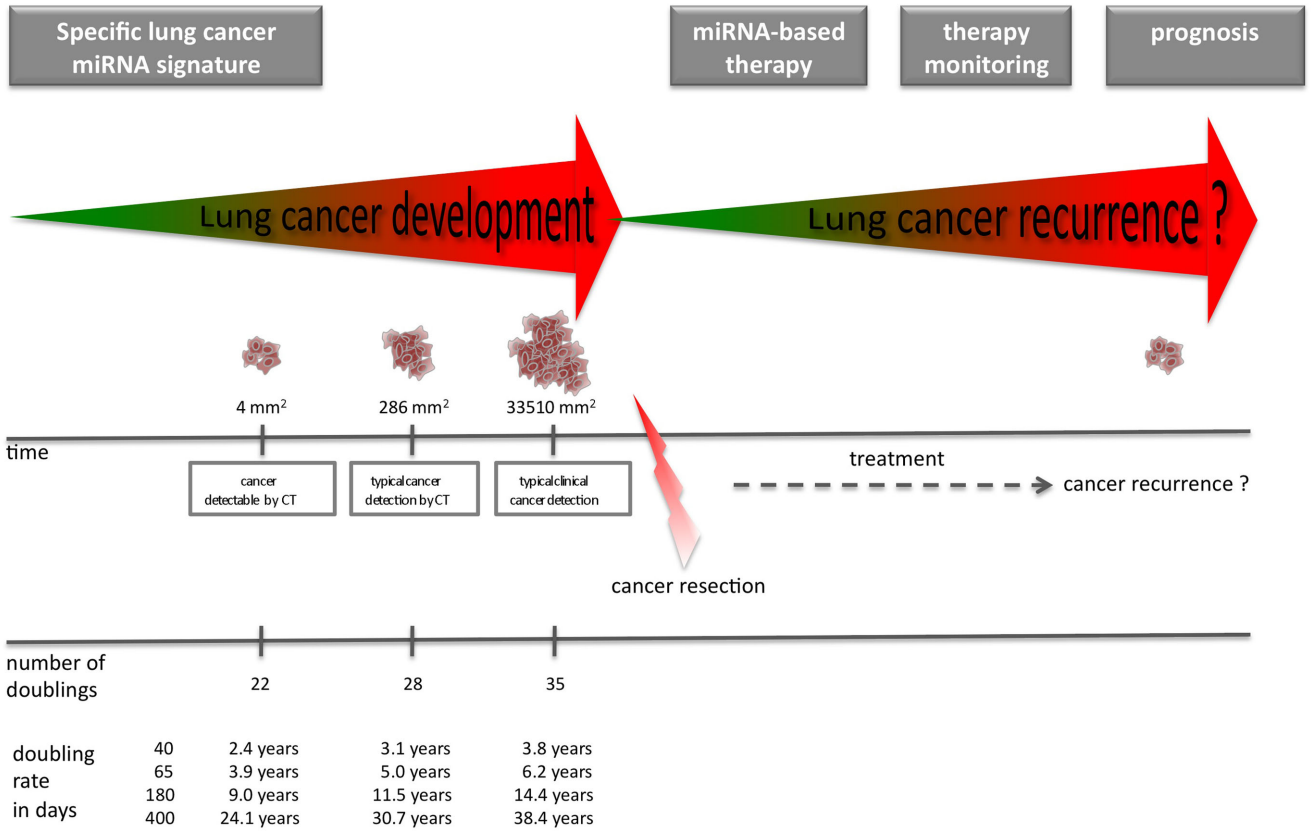

FIGURE 2 | Time points for the application of lung cancer specific miRNAs. Specific tumor-associated miRNA signatures might detect the tumor prior to CT. After cancer resection and/or therapy (radiotherapy or chemotherapy) miRNAs might help in therapy monitoring and prognosis. MiRNAs may also be used for anti-cancer therapy instead of or in combination with radiotherapy or chemotherapy. The timeline at the bottom of the Figure shows the growths rate of a lung tumor with several doubling rates (adapted from Bach et al., 2007).

carcinoma patients from healthy individuals with 73% sensitivity and 96% specificity (Xing et al., 2010).

Since the first study that demonstrated larger amounts of stable miRNAs in serum and plasma, several studies proved that the serum or plasma miRNAs show great promise as novel non-invasive biomarkers for the early diagnosis of various cancers and other diseases (Chen et al., 2008; Mitchell et al., 2008). Chen et al. (2011) identified in a genome-wide serum miRNA expression study a specific panel of 10 miRNAs that was able to distinguish NSCLC cases from controls with high sensitivity and specificity and that correlated with the stage of NSCLC. Furthermore, this 10-serum miRNA profile could accurately classify serum samples collected up to 3 years prior to the clinical NSCLC diagnosis. By expression analysis of two serum miRNAs (hsa-miR-1254 and hsa-miR-574-5p), Foss et al. (2011) were able to discriminate early stage NSCLC samples from controls with a sensitivity of 82% and a specificity of 77% in a training cohort and with a sensitivity of 73% and a specificity of 71% in a validation cohort. Shen et al. (2011) recently identified a panel of four miRNAs namely miR-21, miR-126, miR-210, and miR-486-5p, that distinguished NSCLC patients from the healthy controls with 86.22% sensitivity and 96.55% specificity. Furthermore, the panel of miRNAs identified stage I NSCLC patients with 73.33% sensitivity and 96.55% specificity. Interestingly, two of these miRNAs, namely miR-21 and miR-486, show an overlap with the study on sputum by Yu et al. (2010). Rabinowits et al. (2009) investigated the expression of 12 specific miRNAs including hsa-miR-17-3p, hsa-miR-21, hsa-miR-106a, hsa-miR-146, hsa-miR-155, hsa-miR-191, hsa-miR-192, hsa-miR-203, hsa-miR-205, hsa-miR-210, hsa-miR-212, and hsa-miR-214, in circulating exosomes. The authors suggest that circulating exosomal miRNA might be useful in a screening test for lung adenocarcinoma. In a recent study, we reported serum miRNA profiles as a non-invasive method to detect lung cancer at an early stage (Keller et al., 2011b). We analyzed miRNA signatures in serum from lung cancer patient samples, which were collected prior and after diagnosis. We found that most obvious changes in miRNA expression profiles occur at a time close to diagnosis possibly indicating increased tumor development. Likewise, Boeri et al. (2011) were able to predict lung cancer in plasma samples 1–2 years prior to diagnosis using CT. For the time being, however, the source of circulating miRNAs is elusive. As indicated above it has been suggested that they are released due to apoptosis or active exocytosis processes (Kosaka et al., 2010). This hypothesis is supported by the study by Rabinowits et al. (2009) that showed a similarity between the circulating exosomal miRNA and the lung tumor-derived miRNA patterns. In contrast,

miRNAs deregulated in lung cancer tissue were rarely detected in plasma samples from lung cancer patients in the study of Boeri et al. (2011) that compared the expression of deregulated miRNAs in lung cancer tissue with the expression in plasma specimens. To draw further conclusions about the relationship between miRNA profiles in body fluids and the tumor, more insight is required into both the exact role of miRNAs as molecular regulators in tumor cells and the mechanisms underlying the release of miRNA into body fluids.

miRNAs AS POTENTIAL PROGNOSTIC BIOMARKER FOR LUNG CANCER

Various up- and downregulated miRNAs have been associated with patients' survival. Vosa et al. (2011) showed that low expression of miR-374 could be associated with patients' low survival time. Yanaihara et al. (2006) demonstrated that high expression of hsa-miR-155 and low expression of hsa-let-7a-2 were associated with lung cancer patients' poor survival time. Raponi et al. (2009) showed that miR-146b was associated with reduced survival time in squamous cell carcinoma tissues (SCC). Recently, a study by Landi et al. (2010) presented a miRNA signature including let-7e, miR-34a, miR-34c-5p, miR-25, and miR-191, which was associated with a prognosis of poor survival among male smokers suffering from stage I to IIIa SCC. A miR-21 overexpression in NSCLC that was detected by Markou et al. (2008) has been suggested as future negative prognostic factor. Hu et al. (2010) analyzed miRNA expression profiles in sera of 303 patients with stage I to IIIA NSCLC. They detected miRNA levels altered between patients with shorter survival and longer survival time. Moreover, their results revealed that four miRNAs, including miR-486, miR-30d, miR-1, and miR-499 correlated with overall survival. Furthermore, increased levels of miR-25 and miR-223 in serum may in the future serve as potential markers for NSCLC (Chen et al., 2008). By using microarray, Liu et al. (2011) analyzed the miRNA expression of six paired lung cancer and normal tissues and identified three differentially expressed miRNAs namely miR-21, miR-141, and miR-200c. High expressions of miR-21 and miR-200c in the tumor and of miR-21 in serum were associated with a poor survival in NSCLC patients (Liu et al., 2011).

Although the above studies clearly show that miRNA expression can be associated with patients' survival, the specific miRNAs associated with patient survival differ substantially between studies. These discrepancies are due to (i) different sources of miRNA, i.e., tissue or body fluid, (ii) different methods applied for miRNA analysis, i.e., microarray, qRT-PCR, and deep sequencing, (iii) varying numbers of analyzed miRNAs, and (iv) the criteria used to select patient cohorts, i.e., ethnicity, clinicopathologic features, and therapy. Future studies of miRNA signatures should benefit from largely standardized protocols.

miRNAs AS POTENTIAL THERAPEUTIC AGENT

An increasing number of studies examined the therapeutic potential of miRNAs. Major emphasis is given to the analysis of hsa-let-7, which was the first miRNA associated with lung cancer development (Takamizawa et al., 2004; Johnson et al., 2005, 2007). Exogenous delivery of let-7 inhibited lung cancer growth both in mouse models and in human lung cancer cell lines (Esquela-Kerscher et al., 2008; Trang et al., 2010). As for the therapeutic potential of other miRNAs, a very recent study by Frezzetti et al. (2011) showed that upregulation of miR-21 is controlled by the oncogene RAS and that a locked nucleic acid (LNA) against miR-21 decelerates tumor growth in mice. MiRNA-145 that is known to function as tumor suppressor in several types of cancer (Akao et al., 2007; Porkka et al., 2007; Nam et al., 2008) was recently shown to inhibit cell proliferation in NSCLC cells. Specifically, exogenous miRNA-145 inhibited cell proliferation in NSCLC cells by targeting Myc (Chen et al., 2010). MiR-93, miR-98, and miR-197 all of which are overexpressed in lung cancer, interact with the 3′ UTR of the tumor suppressor gene FUS1. This interaction results in a downregulation of the protein expression making these miRNAs crucial for tumor progression (Du et al., 2009). MiR-128b was shown to directly regulate EGFR in NSCLC cell lines. In addition, loss of heterozygosity of miR-128b was associated with both the clinical response and patients' survival (Weiss et al., 2008). Overexpression of miR-192, which is weakly expressed in lung cancer, resulted in decreased retinoblastoma 1 (*rb1*) mRNA and Rb1 protein expression. These data indicate that miR-192 induces cell apoptosis through the caspase pathway (Feng et al., 2011).

To fully benefit from the large number of miRNAs and their potential targets, computational algorithms like PicTar, miRanda, and Target Scan have been developed to detect adequate miRNA targets (Sethupathy et al., 2006; Backes et al., 2010). In addition, suitable delivery systems are being developed to transport miRNAs or antagomirs – specific oligomers used as miRNA antagonists – to their potential targets (Landen et al., 2005; Shahzad et al., 2011). Antagomirs have been shown to reduce levels of corresponding miRNAs *in vivo* (Krutzfeldt et al., 2005). Using a lipid-based delivery system and chemically synthesized miR-34a, Wiggins et al. (2010) demonstrated growth inhibition of subcutaneous NSCLC cells in mice. The same group used this delivery system in Kras-activated autochthonous mouse models of NSCLC. They found that systemic application of complexes consisting of synthetic miRNA-mimics for let-7 and miR-34a and of the neutral lipid emulsion are preferentially directed to tumor sites and significantly decreased tumor burden (Trang et al., 2011). Most recently, a cationic lipid-based miRNA system was used to condense miRNA miR-133b to form lipoplexes in order to enhance cellular uptake and pharmacological effectiveness *in vitro* and *in vivo* (Wu et al., 2011). As a tumor suppressor that directly targets the pro-survival gene MCL-1, hsa-miR-133b seems to be a potential therapeutic target to influence both cell survival and sensitivity of lung cancer cells to chemotherapeutic agents (Wu et al., 2011). Although these examples underline the therapeutic perspectives of miRNAs, several challenges have to be addressed on the road toward clinical application. First, delivery systems without toxic side effects are required to effectively and selectively transport miRNA-based therapeutics to the tumor site. As of now, lipid-based carrier (Wiggins et al., 2010), nanoparticles (Shi et al., 2011) or viral delivery systems (Zhang et al., 2006), have *in vitro* or *in vivo* been investigated for cancer therapy. Second, the ability of a single miRNA to regulate of up to several 100 targets genes complicates specific targeting and might readily result in unspecific effects. For further information on the therapeutic potential of miRNAs we would like to refer the reader to the reviews of Kasinski and Slack (2011) in Nature Reviews

and McDermott et al. (2011) in Pharmaceutical Research, which provide a comprehensive summary of the current *in vivo* and/or *in vitro* studies.

CONCLUSION

Since their discovery in the 1990s miRNAs have increasingly been recognized as significant not only for the understanding of cancer growth and progression, but also as potential cancer biomarkers. Lung cancer as a disease with poor prognosis and a death toll of thousands of cases per year is one of the prime cancers that call for new markers to allowing early diagnosis. As summarized there is considerable progress in developing miRNA signatures into new biomarkers for lung cancer. MiRNA signatures are likely to contribute to improved early diagnosis, patients' prognosis, or anti-cancer therapy. It is to be, however, recognized, that the overwhelming majority of studies is still in the field of basic science and numerous hurdles need to be overcome before any of the miRNA-based approaches can be introduced in clinical practice. As for cancer detection, the major challenge will be the implementation of standardized protocols for the isolation and the analysis of miRNAs. For cancer therapy, robust and specific delivery systems have to be developed for the transport of miRNAs to the tumor site. Finally, both cancer detection and cancer therapy will greatly benefit from a better understanding of the biological role of miRNAs in cancer cells.

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APPENDIX

Table A1 | Summary of miRNAs associated with lung cancer.

miRNA	miRNA function in lung neoplasia	Reference
hsa-mir-125b-1	Deletion	Calin et al. (2004)
hsa-let-7a-1	Reduced expression, decreased abundance; negatively regulate the RAS gene	Takamizawa et al. (2004)
hsa-let-7a-2	Reduced expression, decreased abundance; negatively regulate the RAS gene	
hsa-let-7a-3	Reduced expression, decreased abundance; negatively regulate the RAS gene	
hsa-let-7b	Reduced expression, decreased abundance; negatively regulate the RAS gene	
hsa-let-7c	Reduced expression, decreased abundance; negatively regulate the RAS gene	
hsa-let-7d	Reduced expression, decreased abundance; negatively regulate the RAS gene	
hsa-let-7e	Reduced expression, decreased abundance; negatively regulate the RAS gene	
hsa-let-7f-1	Reduced expression, decreased abundance; negatively regulate the RAS gene	
hsa-let-7f-2	Reduced expression, decreased abundance; negatively regulate the RAS gene	
hsa-let-7g	Reduced expression, decreased abundance; negatively regulate the RAS gene	
hsa-let-7i	Reduced expression, decreased abundance; negatively regulate the RAS gene	
hsa-mir-17	Overexpressed	Hayashita et al. (2005)
hsa-mir-18a	Overexpressed	
hsa-mir-19a	Overexpressed	
hsa-mir-19b-1	Overexpressed	
hsa-mir-20a	Overexpressed	
hsa-mir-92a-1	Overexpressed	
hsa-mir-128b	Overexpressed	Volinia et al. (2006)
hsa-mir-155	Overexpressed	
hsa-mir-17	Overexpressed	
hsa-mir-191	Overexpressed	
hsa-mir-199a-1	Overexpressed	
hsa-mir-21	Overexpressed	
hsa-mir-101-1	Downregulation	Yanaihara et al. (2006)
hsa-mir-106a	Upregulation	
hsa-mir-124a-1	Downregulation	
hsa-mir-124a-3	Downregulation	
hsa-mir-125a-precursor	Downregulation	
hsa-mir-125a	Downregulation	
hsa-mir-126*	Downregulation	
hsa-mir-126	Downregulation	
hsa-mir-140	Downregulation	
hsa-mir-143	Downregulation	
hsa-mir-145	Downregulation	
hsa-mir-146	Upregulation	
hsa-mir-150	Upregulation	
hsa-mir-155	Upregulation	
hsa-mir-17-3p	Upregulation	
hsa-mir-181c-precursor	Downregulation	
hsa-mir-191	Upregulation	
hsa-mir-192-precursor	Downregulation	
hsa-mir-192	Upregulation	
hsa-mir-197	Upregulaion	
hsa-mir-198	Downregulation	
hsa-mir-199b-precursor	Downregulation	
hsa-mir-203	Upregulation	
hsa-mir-205	Upregulation	
hsa-mir-21	Upregulation	
hsa-mir-210	Upregulation	

(Continued)

Table A1 | Continued

miRNA	miRNA function in lung neoplasia	Reference
hsa-mir-212	Upregulation	
hsa-mir-214	Upregulation	
hsa-mir-216-precursor	Downregulation	
hsa-mir-218-2	Downregulation	
hsa-mir-219-1	Downregulation	
hsa-mir-220	Downregulation	
hsa-mir-224	Downregulation	
hsa-mir-24-2	Upregulation	
hsa-mir-26a-1-precursor	Downregulation	
hsa-mir-27b	Downregulation	
hsa-mir-29b-2	Downregulation	
hsa-mir-30a-5p	Downregulation	
hsa-mir-32	Downregulation	
hsa-mir-33	Downregulation	
hsa-mir-9	Downregulation	
hsa-mir-95	Downregulation	
hsa-let-7a-2-precursor	Downregulation	
hsa-mir-132	miR-132, previously shown to be differentially upregulated in six solid cancer types (breast, colon, lung, pancreas, prostate, and stomach carcinomas)	Lee et al. (2007)
hsa-mir-29a	miR-29 family (29a,b,c) reverts aberrant methylation in lung cancer by targeting DNA methyltransferases 3A and 3B	Fabbri et al. (2007)
hsa-mir-29b-1	miR-29 family (29a,b,c) reverts aberrant methylation in lung cancer by targeting DNA methyltransferases 3A and 3B	
hsa-mir-29c	miR-29 family (29a,b,c) reverts aberrant methylation in lung cancer by targeting DNA methyltransferases 3A and 3B	
hsa-mir-128b	Increased	Weiss et al. (2008)
hsa-mir-126	Inhibits invasion in non-small cell lung carcinoma cell lines	Crawford et al. (2008)
hsa-mir-1	Downregulated	Nasser et al. (2008)
hsa-mir-183	Potential metastasis-inhibitor	Wang et al. (2008)
hsa-let-7a	let-7a: A SNP in a let-7 microRNA complementary site in the KRAS 3′ untranslated region increases non-small cell lung cancer risk	Chin et al. (2008)
hsa-let-7b	let-7b: A SNP in a let-7 microRNA complementary site in the KRAS 3′ untranslated region increases non-small cell lung cancer risk	
hsa-let-7d	let-7d: A SNP in a let-7 microRNA complementary site in the KRAS 3′ untranslated region increases non-small cell lung cancer risk	
hsa-let-7g	let-7g: A SNP in a let-7 microRNA complementary site in the KRAS 3′ untranslated region increases non-small cell lung cancer risk	
hsa-mir-126	Inhibits the growth of lung cancer cell line	Liu et al. (2009a)
hsa-mir-142-5p	Was repressed, overexpression can inhibit lung cancer growth	Liu et al. (2009b)
hsa-mir-145	Was repressed, overexpression can inhibit lung cancer growth	
hsa-mir-34c	Was repressed, overexpression can inhibit lung cancer growth	
hsa-mir-205	Highly specific marker for squamous cell lung carcinoma	Lebanony et al. (2009)
hsa-mir-196a-2	Genetic variant is associated with increased susceptibility of lung cancer in Chinese	Tian et al. (2009)
hsa-miR-21	Upregulated in lung cancer in never-smokers	Seike et al. (2009)
hsa-mir-141	Upregulated in lung cancer in never-smokers	
hsa-mir-210	Upregulated in lung cancer in never-smokers	
hsa-mir-200b	Upregulated in lung cancer in never-smokers	
hsa-mir-346	Upregulated in lung cancer in never-smokers	
hsa-mir-126*	Downregulated in lung cancer in never-smokers	
hsa-mir-126	Downregulated in lung cancer in never-smokers	
hsa-mir-30a	Downregulated in lung cancer in never-smokers	
hsa-mir-30d	Downregulated in lung cancer in never-smokers	

(Continued)

Table A1 | Continued

miRNA	miRNA function in lung neoplasia	Reference
hsa-mir-486	Downregulated in lung cancer in never-smokers	
hsa-mir-129	Downregulated in lung cancer in never-smokers	
hsa-mir-451	Downregulated in lung cancer in never-smokers	
hsa-mir-521	Downregulated in lung cancer in never-smokers	
hsa-mir-138	Downregulated in lung cancer in never-smokers	
hsa-mir-30b	Downregulated in lung cancer in never-smokers	
hsa-mir-30c	Downregulated in lung cancer in never-smokers	
hsa-mir-516a	Downregulated in lung cancer in never-smokers	
hsa-mir-520	Downregulated in lung cancer in never-smokers	
hsa-mir-17-5p	miR-17–92 cluster may contribute to protect SCLC cells carrying RB inactivation from excessive DNA damage and paradoxical growth inhibitory effects, to a large extent by direct downregulation of E2F1 expression. Overexpression involved in fine-tuning ROS generation	Ebi et al. (2009)
hsa-mir-20a	miR-17–92 cluster may contribute to protect SCLC cells carrying RB inactivation from excessive DNA damage and paradoxical growth inhibitory effects, to a large extent by direct downregulation of E2F1 expression. Overexpression involved in fine-tuning ROS generation	
hsa-mir-145	miR-34c, miR-145, or miR-142-5p expression markedly diminished proliferation of lung cancer cell lines, clinical implications discussed	Sempere et al. (2009)
hsa-mir-142-5p	miR-34c, miR-145, or miR-142-5p expression markedly diminished proliferation of lung cancer cell lines, clinical implications discussed	
hsa-mir-34c	miR-34c, miR-145, or miR-142-5p expression markedly diminished proliferation of lung cancer cell lines, clinical implications discussed	
hsa-mir-133b	Low expression, targets pro-survival molecules MCL-1 and BCL-2L2	Crawford et al. (2009)
hsa-mir-98	Regulate tumor suppressor gene FUS1	Du et al. (2009)
hsa-mir-197	Regulate tumor suppressor gene FUS1	
hsa-mir-93	Regulate tumor suppressor gene FUS1	
hsa-mir-185	Cell cycle arrest	Takahashi et al. (2009)
hsa-miR-107	Cell cycle arrest	
hsa-mir-34a	Prognostic marker of relapse in surgically resected non-small cell lung cancer	Gallardo et al. (2009)
hsa-let-7g	let-7g was downregulated in radio-resistant H1299 cells; increased with response to ionizing radiation when knockdown LIN28B	Jeong et al. (2009)
hsa-mir-34a	miR-34a:MicroRNA-34a is an important component of PRIMA-1-induced apoptotic network in human lung cancer cells	Duan et al. (2010)
hsa-mir-133b	Downregulated	Navon et al. (2009)
hsa-mir-486-5p	Downregulated	
hsa-mir-629	Upregulated	
hsa-let-7a	Inhibition of proliferation in non-small cell lung cancer	Zhong et al. (2010)
hsa-mir-126	Inhibition of proliferation in non-small cell lung cancer	
hsa-mir-145	Inhibition of proliferation in non-small cell lung cancer	
hsa-mir-181b	Modulates multidrug resistance by targeting BCL-2 in human cancer cell lines	Zhu et al. (2010a)
hsa-mir-486	Levels of four miRNAs (i.e., miR-486, miR-30d, miR-1, and miR-499) were significantly associated with overall survival	Hu et al. (2010)
hsa-mir-30d	Levels of four miRNAs (i.e., miR-486, miR-30d, miR-1, and miR-499) were significantly associated with overall survival	
hsa-mir-499	Levels of four miRNAs (i.e., miR-486, miR-30d, miR-1, and miR-499) were significantly associated with overall survival	
hsa-mir-1	Levels of four miRNAs (i.e., miR-486, miR-30d, miR-1, and miR-499) were significantly associated with overall survival	
hsa-mir-21	MicroRNA-21 (miR-21) represses tumor suppressor PTEN and promotes growth and invasion in non-small cell lung cancer (NSCLC)	Zhang et al. (2010b)
hsa-mir-136	We found that miR-136, miR-376a, and miR-31 were each prominently overexpressed in murine lung cancers	Liu et al. (2010)

(Continued)

Table A1 | Continued

miRNA	miRNA function in lung neoplasia	Reference
hsa-mir-376a	We found that miR-136, miR-376a, and miR-31 were each prominently overexpressed in murine lung cancers	
hsa-mir-31	We found that miR-136, miR-376a, and miR-31 were each prominently overexpressed in murine lung cancers	
hsa-mir-182	Suppresses lung tumorigenesis through downregulation of RGS17 expression *in vitro*	Sun et al. (2010)
hsa-mir-148a	The silencing of mir-148a production by DNA hypermethylation is an early event in pancreatic carcinogenesis	Hanoun et al. (2010)
hsa-mir-301a	Blocking of miR-301 in A549 cells leads to a decrease in the expression of the host gene, ska2	Cao et al. (2010)
hsa-mir-34a	Development of a lung cancer therapeutic based on the tumor suppressor microRNA-34	Wiggins et al. (2010)
hsa-mir-103	Significant overexpression of miR-103, miR-107, miR-301, and miR-338 in lung cancer cells as compared to HBECs	Du et al. (2010)
hsa-mir-107	Significant overexpression of miR-103, miR-107, miR-301, and miR-338 in lung cancer cells as compared to HBECs	
hsa-mir-301	Significant overexpression of miR-103, miR-107, miR-301, and miR-338 in lung cancer cells as compared to HBECs	
hsa-mir-338	Significant overexpression of miR-103, miR-107, miR-301, and miR-338 in lung cancer cells as compared to HBECs	
hsa-mir-186*	May serve as a potential gene therapy target for refractory lung cancer that is sensitive to curcumin	Zhang et al. (2010a)
hsa-mir-206	Associated with invasion and metastasis of lung cancer	Wang et al. (2010)
hsa-mir-497	Modulates multidrug resistance of human cancer cell lines by targeting BCL-2	Zhu et al. (2010b)
hsa-mir-145	Inhibits cell proliferation of human lung adenocarcinoma by targeting EGFR and NUDT1	Cho et al. (2011)
hsa-mir-638	Upregulation of mir-638 and mir-923 in bostrycin-treated lung adenocarcinoma cells	Chen et al. (2011b)
hsa-mir-923	Upregulation of mir-638 and mir-923 in bostrycin-treated lung adenocarcinoma cells	
hsa-mir-34b	Suppresses the expression of α4 through specific binding to the 3′-untranslated region of α4 is downregulated in transformed or human lung tumors	Chen et al. (2011a)
hsa-let-7a-2	9-cis-RA, all-trans-RA, lithium chloride and CEBPα might play important regulatory roles in let-7a2 gene expression in A549 cells	Guan et al. (2011)
hsa-mir-200	The notch ligand Jagged2 promotes lung adenocarcinoma metastasis through a miR-200-dependent pathway in mice	Yang et al. (2011)
hsa-mir-9	Enhances the sensitivity to ionizing radiation by suppression of NFKB1	Arora et al. (2011a)
hsa-let-7g	Enhances the sensitivity to ionizing radiation by suppression of NFKB1	
hsa-let-7g	Precursor let-7g microRNA can supress A549 lung cancer cell migration	Park et al. (2011)
hsa-mir-145	Suppresses lung adenocarcinoma-initiating cell proliferation by targeting OCT4	Yin et al. (2011)
hsa-mir-196a-2	hsa-miR-196a2 rs11614913 polymorphism may contribute to the susceptibility of cancers. CC genotype might modulate lung cancer risk (OR = 1.25, 95% CI = 1.06–1.46, pheterogeneity = 0.958)	Chu et al. (2011)
hsa-mir-145	Inhibits lung adenocarcinoma stem cells proliferation by targeting OCT4 gene	Zhang et al. (2011b)
hsa-mir-182	Inhibits the proliferation and invasion of human lung adenocarcinoma cells through its effect on human cortical actin-associated protein	Zhang et al. (2011a)
hsa-mir-21	High expression of serum miR-21 associated with poor prognosis in patients with lung cancer	Liu et al. (2011)
hsa-mir-200c	High expression of tumor miR-200c associated with poor prognosis in patients with lung cancer	
hsa-mir-222	High-mobility group A1 proteins enhance the expression of the oncogenic miR-222 in lung cancer cells.	Zhang et al. (2011c)
hsa-mir-155	Could significantly inhibit the growth of human lung cancer 95D cells *in vitro*, which might be closely related to miR-155 induced G0/G1 phase arrest	Qin et al. (2011)

(Continued)

Table A1 | Continued

miRNA	miRNA function in lung neoplasia	Reference
hsa-mir-125a-5p	Induces apoptosis by activating p53 in lung cancer cells	Jiang et al. (2011)
hsa-mir-146b	Overexpression of the Lung Cancer-prognostic miR-146b has a minimal and negative effect on the malignant phenotype of A549 Lung cancer cells	Patnaik et al. (2011)
hsa-mir-101	miR-101 DNA copy loss is a prominent subtype specific event in lung cancer	Thu et al. (2011)
hsa-mir-375	miR-375 is activated by ASH1 and inhibits YAP1 in a lineage dependent manner in lung cancer	Nishikawa et al. (2011)
hsa-mir-26b	Expression of miR-26b was downregulated, and its target activating transcription factor 2 (ATF2) mRNA was up regulated in γ-irradiated H1299 cells	Arora et al. (2011b)
hsa-mir-155	The levels of miR-155, miR-197, and miR-182 in the plasma of lung cancer including stage I patients were significantly elevated compared with controls ($P < 0.001$). The combination of these three miRNAs yielded 81.33% sensitivity and 86.76% specificity in discriminating lung cancer patients from controls. The levels of miR-155 and miR-197 were higher in the plasma from lung cancer patients with metastasis than in those without metastasis ($P < 0.05$) and were significantly decreased in responsive patients during chemotherapy ($P < 0.001$)	Zheng et al. (2011)
hsa-mir-197	The levels of miR-155, miR-197, and miR-182 in the plasma of lung cancer including stage I patients were significantly elevated compared with controls ($P < 0.001$). The combination of these three miRNAs yielded 81.33% sensitivity and 86.76% specificity in discriminating lung cancer patients from controls. The levels of miR-155 and miR-197 were higher in the plasma from lung cancer patients with metastasis than in those without metastasis ($P < 0.05$) and were significantly decreased in responsive patients during chemotherapy ($P < 0.001$)	
hsa-mir-182	The levels of miR-155, miR-197, and miR-182 in the plasma of lung cancer including stage I patients were significantly elevated compared with controls ($P < 0.001$). The combination of these three miRNAs yielded 81.33% sensitivity and 86.76% specificity in discriminating lung cancer patients from controls. The levels of miR-155 and miR-197 were higher in the plasma from lung cancer patients with metastasis than in those without metastasis ($P < 0.05$) and were significantly decreased in responsive patients during chemotherapy ($P < 0.001$)	
hsa-mir-183	Expression levels of members of the miR-183 family in lung cancer tumor and sera were higher than that of their normal counterparts. The miR-96 expression in tumors was positively associated with its expression in sera. High expression of tumor and serum miRNAs of the miR-183 family were associated with overall poor survival in patients with lung cancer	Zhu et al. (2011)
hsa-mir-96	Expression levels of members of the miR-183 family in lung cancer tumor and sera were higher than that of their normal counterparts. The miR-96 expression in tumors was positively associated with its expression in sera. High expression of tumor and serum miRNAs of the miR-183 family were associated with overall poor survival in patients with lung cancer	
hsa-mir-150	Anti-miR-150 vector can regress A549 lung cancer tumors	Li et al. (2011)
hsa-mir-200b	Stably expressing microRNA-200b in As-p53lowHBECs (human bronchial epithelial cell) abolished Akt and Erk1/2 activation, and completely suppressed cell migration and invasion	Wang et al. (2011b)
hsa-mir-9	Upregulated in NSCLC compared to non-tumorous tissue	Vosa et al. (2011)
hsa-mir-182	Upregulated in NSCLC compared to non-tumorous tissue	
hsa-mir-200a +	Upregulated in NSCLC compared to non-tumorous tissue	
hsa-mir-151	Upregulated in NSCLC compared to non-tumorous tissue	
hsa-mir-205	Upregulated in NSCLC compared to non-tumorous tissue	
hsa-mir-183	Upregulated in NSCLC compared to non-tumorous tissue	
hsa-mir-130b*	Upregulated in NSCLC compared to non-tumorous tissue	
hsa-mir-149	Upregulated in NSCLC compared to non-tumorous tissue	
hsa-mir-193b	Upregulated in NSCLC compared to non-tumorous tissue	
hsa-mir-339-5p	Upregulated in NSCLC compared to non-tumorous tissue	
hsa-mir-196b	Upregulated in NSCLC compared to non-tumorous tissue	
hsa-mir-224	Upregulated in NSCLC compared to non-tumorous tissue	
hsa-mir-31	Upregulated in NSCLC compared to non-tumorous tissue	
hsa-mir-196a	Upregulated in NSCLC compared to non-tumorous tissue	
hsa-mir-423-3p	Upregulated in NSCLC compared to non-tumorous tissue	
hsa-mir-708	Upregulated in NSCLC compared to non-tumorous tissue	

(Continued)

Table A1 | Continued

miRNA	miRNA function in lung neoplasia	Reference
hsa-mir-106b*	Upregulated in NSCLC compared to non-tumorous tissue	
hsa-mir-210	Upregulated in NSCLC compared to non-tumorous tissue	
hsa-mir-1273	Downregulated in NSCLC compared to non-tumorous tissue	
hsa-mir-206	Downregulated in NSCLC compared to non-tumorous tissue	
hsa-mir-140-3p	Downregulated in NSCLC compared to non-tumorous tissue	
hsa-mir-338-3p	Downregulated in NSCLC compared to non-tumorous tissue	
hsa-mir-101	Downregulated in NSCLC compared to non-tumorous tissue	
hsa-mir-144	Downregulated in NSCLC compared to non-tumorous tissue	
hsa-mir-1285	Downregulated in NSCLC compared to non-tumorous tissue	
hsa-mir-130a	Downregulated in NSCLC compared to non-tumorous tissue	
hsa-mir-486-5p	Downregulated in NSCLC compared to non-tumorous tissue	
hsa-mir-24-2*	Downregulated in NSCLC compared to non-tumorous tissue	
hsa-mir-144*	Downregulated in NSCLC compared to non-tumorous tissue	
hsa-mir-30a	Downregulated in NSCLC compared to non-tumorous tissue	
hsa-mir-20a	Upregulated in NSCLC serum compared to control serum	Chen et al. (2011c)
hsa-mir-24	Upregulated in NSCLC serum compared to control serum	
hsa-mir-25	Upregulated in NSCLC serum compared to control serum	
hsa-mir-145	Upregulated in NSCLC serum compared to control serum	
hsa-mir-152	Upregulated in NSCLC serum compared to control serum	
hsa-mir-199a-5p	Upregulated in NSCLC serum compared to control serum	
hsa-mir-221	Upregulated in NSCLC serum compared to control serum	
hsa-mir-222	Upregulated in NSCLC serum compared to control serum	
hsa-mir-223	Upregulated in NSCLC serum compared to control serum	
hsa-mir-320	Upregulated in NSCLC serum compared to control serum	
hsa-mir-126	Upregulated in radiotherapy sensitive patients compared to resistant patients of non-small cell lung cancer	Wang et al. (2011a)
hsa-mir-let-7a	Upregulated in radiotherapy sensitive patients compared to resistant patients of non-small cell lung cancer	
hsa-mir-495	Upregulated in radiotherapy sensitive patients compared to resistant patients of non-small cell lung cancer	
hsa-mir-451	Upregulated in radiotherapy sensitive patients compared to resistant patients of non-small cell lung cancer	
hsa-mir-128b	Upregulated in radiotherapy sensitive patients compared to resistant patients of non-small cell lung cancer	
hsa-mir-130a	Downregulated in radiotherapy sensitive patients compared to resistant patients of non-small cell lung cancer	
hsa-mir-106b	Downregulated in radiotherapy sensitive patients compared to resistant patients of non-small cell lung cancer	
hsa-mir-19b	Downregulated in radiotherapy sensitive patients compared to resistant patients of non-small cell lung cancer	
hsa-mir-22	Downregulated in radiotherapy sensitive patients compared to resistant patients of non-small cell lung cancer	
hsa-mir-15b	Downregulated in radiotherapy sensitive patients compared to resistant patients of non-small cell lung cancer	
hsa-mir-17-5p	Downregulated in radiotherapy sensitive patients compared to resistant patients of non-small cell lung cancer	
hsa-mir-21	Downregulated in radiotherapy sensitive patients compared to resistant patients of non-small cell lung cancer	
hsa-miR-126	Downregulated in lung SCC compared to normal lung tissues	Yang et al. (2010)
hsa-miR-193a-3p	Downregulated in lung SCC compared to normal lung tissues	
hsa-miR-30d	Downregulated in lung SCC compared to normal lung tissues	
hsa-miR-30a	Downregulated in lung SCC compared to normal lung tissues	

(Continued)

Table A1 | Continued

miRNA	miRNA function in lung neoplasia	Reference
hsa-miR-101	Downregulated in lung SCC compared to normal lung tissues	
hsa-let-7i	Downregulated in lung SCC compared to normal lung tissues	
hsa-miR-15a	Downregulated in lung SCC compared to normal lung tissues	
hsa-miR-185 *	Upregulated in lung SCC compared to normal lung tissues	
hsa-miR-125a-5p	Upregulated in lung SCC compared to normal lung tissues	
hsa-let-7f	Decreased in plasma vesicles from 28 NSCLC patients and 20 controls. Plasma levels of mir-30e-3p and let-7f were associated with short disease-free survival and overall survival	Silva et al. (2011)
hsa-miR-20b	Decreased in plasma vesicles from 28 NSCLC patients and 20 controls	
hsa-miR-30e-3p	Decreased in plasma vesicles from 28 NSCLC patients and 20 controls. Plasma levels of mir-30e-3p and let-7f were associated with short disease-free survival and overall survival	
hsa-miR-21	Overexpressed in cell lines for breast cancer, prostate cancer, glioblastoma, and lung cancer	Roa et al. (2010)
hsa-miR-182	Overexpressed in cell lines for breast cancer, prostate cancer, glioblastoma, and lung cancer	
hsa-let-7-5a	Underexpressed in cell lines for breast cancer, prostate cancer, glioblastoma, and lung cancer	
hsa-miR-145	Underexpressed in cell lines for breast cancer, prostate cancer, glioblastoma, and lung cancer	
hsa-miR-155		
hsa-miR-21	Upregulated in lung carcinoma tissues and their corresponding normal lung tissues, high mir-21 expression and low mir-181a expression were associated with poor survival, independent of clinical covariates, including TNM staging, lymph note status	Gao et al. (2010)
hsa-mir-143	Downregulated in lung carcinoma tissues and their corresponding normal lung tissues, low level expression of mir-143 was significantly correlated with smoking status	
hsa-mir-181a	Downregulated in lung carcinoma tissues and their corresponding normal lung tissues, high mir-21 expression and low mir-181a expression were associated with poor survival, independent of clinical covariates, including TNM staging, lymph note status	
hsa-let-7g	Upregulated in adenocarcinoma compared to squamous cell carcinoma	Landi et al. (2010)
hsa-let-7b	Upregulated in adenocarcinoma compared to squamous cell carcinoma	
hsa-let-7c	Upregulated in adenocarcinoma compared to squamous cell carcinoma	
hsa-miR-29a	Upregulated in adenocarcinoma compared to squamous cell carcinoma	
hsa-let-7f	Upregulated in adenocarcinoma compared to squamous cell carcinoma	
has-miR-453	Downregulated in adenocarcinoma compared to squamous cell carcinoma	
hsa-let-7d	Upregulated in adenocarcinoma compared to squamous cell carcinoma	
hsa-miR-98	Upregulated in adenocarcinoma compared to squamous cell carcinoma	
hsa-let-7i	Upregulated in adenocarcinoma compared to squamous cell carcinoma	
hsa-miR-26a	Upregulated in adenocarcinoma compared to squamous cell carcinoma	
hsa-miR-509-3p	Downregulated in adenocarcinoma compared to squamous cell carcinoma	
hsa-miR-30b	Upregulated in adenocarcinoma compared to squamous cell carcinoma	
hsa-miR-146b-5p	Upregulated in adenocarcinoma compared to squamous cell carcinoma	
hsa-miR-106b	Upregulated in adenocarcinoma compared to squamous cell carcinoma	
hsa-let-7a	Upregulated in adenocarcinoma compared to squamous cell carcinoma	
hsa-mir-663	Upregulated in adenocarcinoma compared to squamous cell carcinoma	
hsa-miR-30d	Upregulated in adenocarcinoma compared to squamous cell carcinoma	
hsa-miR-17	Upregulated in adenocarcinoma compared to squamous cell carcinoma	
hsa-miR-498	Upregulated in adenocarcinoma compared to squamous cell carcinoma	
hsa-miR-26b	Upregulated in adenocarcinoma compared to squamous cell carcinoma	
hsa-let-7e	Upregulated in adenocarcinoma compared to squamous cell carcinoma	
hsa-mir-654-5p	Upregulated in adenocarcinoma compared to squamous cell carcinoma	
hsa-miR-181a	Upregulated in adenocarcinoma compared to squamous cell carcinoma	
hsa-miR-103	Upregulated in adenocarcinoma compared to squamous cell carcinoma	
hsa-miR-195	Upregulated in adenocarcinoma compared to squamous cell carcinoma	
hsa-miR-191	Upregulated in adenocarcinoma compared to squamous cell carcinoma	
hsa-miR-20a	Upregulated in adenocarcinoma compared to squamous cell carcinoma	
hsa-miR-106a	Upregulated in adenocarcinoma compared to squamous cell carcinoma	
hsa-miR-29c	Upregulated in adenocarcinoma compared to squamous cell carcinoma	

(Continued)

Table A1 | Continued

miRNA	miRNA function in lung neoplasia	Reference
hsa-miR-29b	Upregulated in adenocarcinoma compared to squamous cell carcinoma	
hsa-miR-491-5p	Upregulated in adenocarcinoma compared to squamous cell carcinoma	
hsa-miR-19b	Upregulated in adenocarcinoma compared to squamous cell carcinoma	
hsa-miR-107	Upregulated in adenocarcinoma compared to squamous cell carcinoma	
hsa-miR-16	Upregulated in adenocarcinoma compared to squamous cell carcinoma	
hsa-mir-129-5p	Underexpressed in recurrence vs. No recurrence case groups of stage I NSCLC	Patnaik et al. (2010)
hsa-mir-194	Underexpressed in recurrence vs. No recurrence case groups of stage I NSCLC	
hsa-mir-631	Underexpressed in recurrence vs. No recurrence case groups of stage I NSCLC	
hsa-mir-200b	Underexpressed in recurrence vs. No recurrence case groups of stage I NSCLC	
hsa-mir-585	Underexpressed in recurrence vs. No recurrence case groups of stage I NSCLC	
hsa-mir-623	Underexpressed in recurrence vs. No recurrence case groups of stage I NSCLC	
hsa-mir-617	Underexpressed in recurrence vs. No recurrence case groups of stage I NSCLC	
hsa-mir-622	Underexpressed in recurrence vs. No recurrence case groups of stage I NSCLC	
hsa-mir-638	Underexpressed in recurrence vs. No recurrence case groups of stage I NSCLC	
hsa-mir-24	Overexpressed in recurrence vs. No recurrence case groups of stage I NSCLC	
hsa-mir-141	Overexpressed in recurrence vs. No recurrence case groups of stage I NSCLC	
hsa-mir-27b	Overexpressed in recurrence vs. No recurrence case groups of stage I NSCLC	
hsa-mir-16	Overexpressed in recurrence vs. No recurrence case groups of stage I NSCLC	
hsa-mir-21	Overexpressed in recurrence vs. No recurrence case groups of stage I NSCLC	
hsa-mir-30c	Overexpressed in recurrence vs. No recurrence case groups of stage I NSCLC	
hsa-mir-106a	Overexpressed in recurrence vs. No recurrence case groups of stage I NSCLC	
hsa-mir-15b	Overexpressed in recurrence vs. No recurrence case groups of stage I NSCLC	
hsa-mir-23b	Overexpressed in recurrence vs. No recurrence case groups of stage I NSCLC	
hsa-mir-23b	Overexpressed in recurrence vs. No recurrence case groups of stage I NSCLC	
hsa-mir-130a	Overexpressed in recurrence vs. No recurrence case groups of stage I NSCLC	
hsa-mir-636	Changed more than twofold by radiation doses of 20Gy	Shin et al. (2009)
hsa-mir-593	Changed more than twofold by radiation doses of 20Gy	
hsa-mir-760	Changed more than twofold by radiation doses of 20Gy	
hsa-mir-139-3p	Changed more than twofold by radiation doses of 20Gy	
hsa-mir-345	Changed more than twofold by radiation doses of 20Gy and 40Gy	
hsa-mir-885-3p	Changed more than twofold by radiation doses of 20Gy and 40Gy	
hsa-mir-206	Changed more than twofold by radiation doses of 20Gy and 40Gy	
hsa-mir-516a-5p	Changed more than twofold by radiation doses of 20Gy and 40Gy	
hsa-mir-16-2*	Changed more than twofold by radiation doses of 20Gy and 40Gy	
hsa-mir-106a	Changed more than twofold by radiation doses of 20Gy and 40Gy	
hsa-mir-548c-3p	Changed more than twofold by radiation doses of 20Gy and 40Gy	
hsa-mir-127-3p	Changed more than twofold by radiation doses of 20Gy and 40Gy	
hsa-mir-1228*	Changed more than twofold by radiation doses of 40Gy	
hsa-mir-30b*	Changed more than twofold by radiation doses of 40Gy	
hsa-mir-376a	Changed more than twofold by radiation doses of 40Gy	
hsa-mir-34b*	Changed more than twofold by radiation doses of 40Gy	
hsa-mir-215	Changed more than twofold by radiation doses of 40Gy	
hsa-mir-183	Changed more than twofold by radiation doses of 40Gy	
hsa-mir-22*	Changed more than twofold by radiation doses of 40Gy	
hsa-mir-34a	Changed more than twofold by radiation doses of 40Gy	
hsa-mir-192	Changed more than twofold by radiation doses of 40Gy	
hsa-mir-30c-1*	Changed more than twofold by radiation doses of 40Gy	
hsa-mir-21	Mir-21 expression in the sputum specimens was significantly higher in cancer patients than cancer-free individuals. overexpression of mir-21 showed highly discriminative receiver-operator characteristic (ROC) curve profile, clearly distinguishing cancer patients from cancer-free subjects Detection of mir-21 expression produced 69.66% sensitivity and 100.00% specificity in diagnosis of lung cancer, as compared with 47.82% sensitivity and 100.00% specificity by sputum cytology	Xie et al. (2010)

(Continued)

Table A1 | Continued

miRNA	miRNA function in lung neoplasia	Reference
hsa-mir-140-3p	Expression of 13 miRNA genes predicts response to EGFR inhibition in cancer cell lines and tumors, and discriminates primary from metastatic tumors	Bryant et al. (2011)
hsa-mir-628-5p	Expression of 13 miRNA genes predicts response to EGFR inhibition in cancer cell lines and tumors, and discriminates primary from metastatic tumors	
hsa-mir-518f	Expression of 13 miRNA genes predicts response to EGFR inhibition in cancer cell lines and tumors, and discriminates primary from metastatic tumors	
hsa-mir-636	Expression of 13 miRNA genes predicts response to EGFR inhibition in cancer cell lines and tumors, and discriminates primary from metastatic tumors	
hsa-mir-301a	Expression of 13 miRNA genes predicts response to EGFR inhibition in cancer cell lines and tumors, and discriminates primary from metastatic tumors	
hsa-mir-34c	Expression of 13 miRNA genes predicts response to EGFR inhibition in cancer cell lines and tumors, and discriminates primary from metastatic tumors	
hsa-mir-224	Expression of 13 miRNA genes predicts response to EGFR inhibition in cancer cell lines and tumors, and discriminates primary from metastatic tumors	
hsa-mir-197	Expression of 13 miRNA genes predicts response to EGFR inhibition in cancer cell lines and tumors, and discriminates primary from metastatic tumors	
hsa-mir-205	Expression of 13 miRNA genes predicts response to EGFR inhibition in cancer cell lines and tumors, and discriminates primary from metastatic tumors	
hsa-mir-135b	Expression of 13 miRNA genes predicts response to EGFR inhibition in cancer cell lines and tumors, and discriminates primary from metastatic tumors	
hsa-mir-200b	Expression of 13 miRNA genes predicts response to EGFR inhibition in cancer cell lines and tumors, and discriminates primary from metastatic tumors	
hsa-mir-200c	Expression of 13 miRNA genes predicts response to EGFR inhibition in cancer cell lines and tumors, and discriminates primary from metastatic tumors	
hsa-mir-141	Expression of 13 miRNA genes predicts response to EGFR inhibition in cancer cell lines and tumors, and discriminates primary from metastatic tumors	
hsa-mir-182	Overexpressed in primary lung tumors vs. metastases to lung	Barshack et al. (2010)
hsa-mir-126	Underexpressed in primary lung tumors vs. metastases to lung	
hsa-mir-200c	Overexpressed in primary lung tumors vs. metastases to lung	
hsa-mir-141	Overexpressed in primary lung tumors vs. metastases to lung	
hsa-mir-375	Overexpressed in primary lung tumors vs. metastases to lung	
hsa-mir-7	Overexpressed in primary lung tumors vs. metastases to lung	
hsa-mir-429	Overexpressed in primary lung tumors vs. metastases to lung	
hsa-mir-200a	Overexpressed in primary lung tumors vs. metastases to lung	
hsa-mir-370	Overexpressed in primary lung tumors vs. metastases to lung	
hsa-mir-451	Underexpressed in primary lung tumors vs. metastases to lung	
hsa-mir-195	Underexpressed in primary lung tumors vs. metastases to lung	
hsa-mir-200b	Overexpressed in primary lung tumors vs. metastases to lung	
hsa-mir-486-5p	Underexpressed in primary lung tumors vs. metastases to lung	
hsa-mir-214	Underexpressed in primary lung tumors vs. metastases to lung	
hsa-mir-382	Overexpressed in primary lung tumors vs. metastases to lung	
hsa-mir-199a-5p	Underexpressed in primary lung tumors vs. metastases to lung	
hsa-mis-210	Upregulated in lung SCC compared to normal tissue	Raponi et al. (2009)
hsa-mir-200c	Upregulated in lung SCC compared to normal tissue	
hsa-mir-17-5p	Upregulated in lung SCC compared to normal tissue	
hsa-mir-20a	Upregulated in lung SCC compared to normal tissue	
hsa-mir-203	Upregulated in lung SCC compared to normal tissue	
hsa-mir-125a	Downregulated in lung SCC compared to normal tissue	
hsa-let-7e	Downregulated in lung SCC compared to normal tissue	
hsa-mir-200a	Upregulated in lung SCC compared to normal tissue	
hsa-mir-106b	Upregulated in lung SCC compared to normal tissue	
hsa-mir-93	Upregulated in lung SCC compared to normal tissue	

(Continued)

Table A1 | Continued

miRNA	miRNA function in lung neoplasia	Reference
hsa-mir-182	Upregulated in lung SCC compared to normal tissue	
hsa-mir-183	Upregulated in lung SCC compared to normal tissue	
hsa-mir-106a	Upregulated in lung SCC compared to normal tissue	
hsa-mir-20b	Upregulated in lung SCC compared to normal tissue	
hsa-mir-224	Upregulated in lung SCC compared to normal tissue	
hsa-miR-126	Downregulated in NSCLC blood compared to normal blood	Keller et al. (2009)
hsa-miR-423-5p	Upregulated in NSCLC blood compared to normal blood	
hsa-let-7d	Downregulated in NSCLC blood compared to normal blood	
hsa-let-7i	Downregulated in NSCLC blood compared to normal blood	
hsa-miR-15a	Downregulated in NSCLC blood compared to normal blood	
hsa-miR-22	Upregulated in NSCLC blood compared to normal blood	
hsa-miR-98	Downregulated in NSCLC blood compared to normal blood	
hsa-miR-19a	Upregulated in NSCLC blood compared to normal blood	
hsa-miR-20b	Downregulated in NSCLC blood compared to normal blood	
hsa-miR-324-3p	Upregulated in NSCLC blood compared to normal blood	
hsa-miR-574-5p	Upregulated in NSCLC blood compared to normal blood	
hsa-miR-195	Downregulated in NSCLC blood compared to normal blood	
hsa-miR-25	Upregulated in NSCLC blood compared to normal blood	
hsa-let-7e	Downregulated in NSCLC blood compared to normal blood	
hsa-let-7c	Downregulated in NSCLC blood compared to normal blood	
hsa-let-7f	Downregulated in NSCLC blood compared to normal blood	
hsa-let-7a	Downregulated in NSCLC blood compared to normal blood	
hsa-let-7g	Downregulated in NSCLC blood compared to normal blood	
hsa-miR-140-3p	Upregulated in NSCLC blood compared to normal blood	
hsa-miR-339-5p	Upregulated in NSCLC blood compared to normal blood	
hsa-miR-361-5p	Upregulated in NSCLC blood compared to normal blood	
hsa-miR-1283	Downregulated in NSCLC blood compared to normal blood	
hsa-miR-18a*	Upregulated in NSCLC blood compared to normal blood	
hsa-miR-26b	Downregulated in NSCLC blood compared to normal blood	
hsa-miR-641	Downregulated in lung cancer vs. COPD	Leidinger et al. (2011)
hsa-miR-662	Upregulated in lung cancer vs. COPD	
hsa-miR-369-5p	Downregulated in lung cancer vs. COPD	
hsa-miR-383	Downregulated in lung cancer vs. COPD	
hsa-miR-636	Upregulated in lung cancer vs. COPD	
hsa-miR-940	Upregulated in lung cancer vs. COPD	
hsa-miR-26a	Downregulated in lung cancer vs. COPD	
hsa-miR-92a	Upregulated in lung cancer vs. COPD	
hsa-miR-328	Upregulated in lung cancer vs. COPD	
hsa-let-7d*	Upregulated in lung cancer vs. COPD	
hsa-miR-1224-3p	Upregulated in lung cancer vs. COPD	
hsa-miR-513b	Downregulated in lung cancer vs. COPD	
hsa-miR-93*	Upregulated in lung cancer vs. COPD	
hsa-miR-675	Upregulated in lung cancer vs. COPD	

This table only includes a selection of available publications.

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