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MicroRNAs and lung cancers: from pathogenesis to clinical implications

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Abstract

Lung cancer is the leading cause of cancer-related deaths in the US and worldwide. Better understanding of the disease is warranted for improvement in clinical management. Here we summarize the functions of small-RNA-based, posttranscriptional gene regulators, i.e. microRNAs, in the pathogenesis of lung cancers. We discuss the microRNAs that play oncogenic as well as tumor suppressive roles. We also touch on the value of microRNAs as markers for diagnosis, prognosis and the promising field of microRNA-based novel therapies for lung cancers.

Keywords

lung biology; lung cancer; microRNA

Introduction

Lung cancer has been the most fatal type of all cancers in the US for both males and females in recent decades. In the most recent statistical data from the American Cancer Society (ACS), lung and bronchus cancers are again estimated to cause the largest number of cancer-related deaths, accounting for 28% and 26% of estimated cancer deaths for US males and females respectively [1]. Globally, lung and bronchus cancers were also the most commonly diagnosed and most fatal cancers in males, while having the fourth highest incidence rate and second highest mortality rate in females [2]. Therefore, molecular studies aiming at early detection and targeted treatment of lung cancers draw intensive research interest.

MicroRNAs (miRNAs) are a group of non-coding RNA (~22nt) posttranscriptional regulators for gene expression [3]. The canonical pathway for miRNA biogenesis starts from transcription by RNA polymerase II. The resultant primary transcript pri-miRNA is cleaved by RNase III endonuclease Drosha, together with its cofactor DGCR8 [4], to generate the ~70nt long pre-miRNA. This hairpin structured transcript will be transported out of the nucleus to the cytoplasm by Exportin 5, and further processed there by another RNase III endonuclease Dicer and its cofactors to a double-stranded form. In most cases, one of the strands is selectively bound by Argonaut proteins [5] to enter the RNA induced silencing complex (RISC) while the complementary one is degraded [6]. But for some miRNAs [7], both strands can be functional. The two mature miRNAs derived from one stem loop are termed miRNA and miRNA* (or miR-5p and miR-3p), respectively. Individual mature

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miRNA sequences can be generated from one or more genes in the genome. The miRNA in the RISC complex recognizes target genes based on sequence complementarity primarily to the 3′ untranslated region (UTR) of target mRNAs. This binding of the RISC complex to the 3′UTR of a target RNA may result in translational inhibition or mRNA degradation [3]. Occasionally, miRNAs can bind to other regions of a mRNA in the protein-coding sequences [8] or 5′ UTR [9]. In selected cases, miRNAs were found to upregulate expression of target genes [10].

Significant progress has been made since Victor Ambros and colleagues discovered the first miRNA (lin-4) in 1993 [11]. In the latest release of the miRbase database (http://www.mirbase.org), there are 21643 mature miRNAs in 168 species. The functional importance of miRNAs is highlighted by their unique capability to simultaneously regulate multiple genes or pathways thus affecting a whole network of biological processes [12]. Since the first report of aberrant miRNA expression in cancers [13], these small RNAs are now realized to be key regulators for tumor pathogenesis and markers for novel clinical interventions. Here we review the roles that miRNAs play in the realm of lung cancers, either pro- or anti-oncogenic, and their potentials for clinical applications.

1. Oncogenic miRNAs in lung cancers

1.1 miR-17~92 cluster

This polycistronic miRNA cluster is encoded by a gene located at 13q31.3 and is comprised of 6 mature miRNA species: miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, and miR-92a-1 [14, 15]. Recently there are also some miRNA* species identified from the complementary strands of the above miRNAs [14]. The miR-17~92 cluster is also designated as oncomir-1 [16] and found to exhibit oncogenic behavior in multiple types of cancers including B-cell lymphoma, breast cancer, colon cancer, pancreatic cancer, glioblastoma, and retinoblastoma [17-22], etc. MiR-17~92 was found oncogenic first by the Hannon group [16]. However, the first piece of evidence that connected miR-17~92 to lung cancers was from the Takahashi group [19]. They showed that this cluster was markedly overexpressed in lung cancer cells and introduction of this miRNA clusterinto lung cancer cells enhanced cell growth. The Takahashi group later revealed that inhibition of miR-17-5p and miR-20a with antisense oligonucleotides induced apoptosis selectively in lung cancer cells overexpressing miR-17~92, suggesting “oncomiR addiction” [23]. The overexpression of members of this cluster in lung cancers was detected by microRNA profiling studies [24]. The expression of miR-17~92 is subject to transactivation by E2F family members [25] and MYC [26], with the latter frequently overexpressed in small cell lung cancers (SCLC) [27]. *HIF-1α* is a direct target of miR-17~92 identified in lung cancers [28]. This relationship in part explained the downregulation of HIF-1α by MYC. In lung cancer cellular context, this regulation affects cell proliferation under normoxia condition without influencing cellular adaptation for hypoxia. Overexpression of miR-17~92 counterbalances γ-HAX2 foci formation and reactive oxygen species (ROS) induced by knocking down the *RB* gene in *RB* wild-type lung cancer cells, suggesting a role of miR-17~92 in fine-tuning the DNA damage level in cancer cells to maintain genomic instability [29]. In order to identify other targets for miR-17~92, a proteomic approach was used in the SBC-3 SCLC cell line, which identified the RAS-related protein 14 (*RAB14*) as a direct target [30]. Since *RAB14* silencing decreased surfactant secretion in the lung [31], downregulation of *RAB14* by miR-17~92 was proposed to unguard the lung against external carcinogens, thus leading to cancer initiation and development [30]. Other targets identified for this cluster include *E2F1-3, BIM, PTEN, TGFBR2, TSP1, CTGF* and *TNF-α* [24, 25, 32–34], together with the above mentioned targets specifically studied in lung cancers rendering miR-17~92 a multifaceted oncomiR regulating cell growth and death, cell cycle progression, and angiogenesis processes in tumorigenesis.

1.2 miR-21

The miR-21 gene locates at chromosome 17 and is one of the more studied oncomiRs across cancer types. In 2006, a miRNA profiling study found that miR-21 was upregulated in all six types of solid tumors analyzed including lung cancers [24]. An antisense oligonuceotide against miR-21 inhibited growth of lung cancer cell line A549 [35]. MiRNA expression analysis of tumors derived from never-smoker lung cancer patients detected miR-21 overexpression and this overexpression was more pronounced in epidermal growth factor receptor (*EGFR*) gene mutant cases than in wild type cases [36]. MiR-21 level was correlated with phosphorylated EGFR (p-EGFR) level and was suppressed by EGFR tyrosine kinase inhibitors (EGFR-TKI). Antisense miR-21 enhanced EGFR-TKI induced apoptosis, with the level depending on the p-EGFR level in the host cell lines. All these data suggest miR-21 as an antiapoptotic factor regulated by the EGFR signaling pathway in lung cancers [36]. The *PTEN* tumor suppressor gene (TSG) was identified as a direct target of miR-21 and repression of this target by miR-21 promoted cell growth and invasion of non-small cell lung cancer (NSCLC) [37]. The mouse model-based study by Hatley et al. clearly demonstrated the oncogenicity of miR-21 in lung cancers [38]. MiR-21 overexpression in *K-ras*^{LA2} mice increased tumor proliferation, while miR-21 deletion in the same lung tumor mouse model suppressed tumor development. They also validated multiple predicted miR-21 targets including negative regulators of the RAS/MEK/ERK pathway: *Spry1, Spry2, Btg2,* and *Pdcd4*. Several pro-apoptotic targets of miR-21 were also identified: *Apaf1, Faslg, RhoB,* and *Pdcd4*. Research by Frezetti et al. [39] in thyroid and lung cancers confirmed miR-21 upregulation by RAS *in vivo* and showed that this upregulation requires activation of two downstream pathways: RAF/MAPK and PI3K. They found that the predicted targets of miR-21 were enriched in the regulators for cell cycle checkpoints. This finding highlights the role of miR-21 in cell cycle regulation. FOXO3a was reported to transcriptionally repress the expression of miR-21 and affect apoptosis in lung cancer cells [40]. Besides RAS and FOXO3a, miR-21 was also found to be regulated by IL-6 in multiple myeloma cells [41], IFN in prostate cancer cells [42], HER2/*neu* in breast cancer cell lines [43], and AP-1 in multiple types of cancer cells at the transcription level [44]. Posttranscriptionally, miR-21 is regulated by type I collagen in lung and breast cancer cells [45], PTEN in glioblastoma cells [46], and TGF-β in breast cancer cell lines [47]. Targets of miR-21 identified outside lung cancers include *TPM1* and *MASPRIN*, which mediate tumor invasion and metastasis [48].

1.3 miR-221/222

The Apo2L/TNF-α-related apoptosis-inducing ligand (TRAIL) is a relatively new member of the TNF family known to induce apoptosis in a variety of cancers [49] and TRAIL based therapy is a promising anti-tumor agent in clinical trials [50]. In a study to identify miRNA expression signatures in TRAIL resistant NSCLC cells, upregulation of miR-221/222 was seen in NSCLC cells resistant to TRAIL [51]. MiR-221 and miR-222 are expressed from the same gene cluster on the X chromosome. They share an identical seed sequence and have overlapping targets by prediction. Introduction of inhibitors to miR-221/222 into TRAIL-resistant cells increased TRAIL sensitivity. Two genes were identified as targets of miR-221/222: *Kit* and *p27*^{Kip1}. In NSCLC cells, a decrease in the level of p27^{Kip1} seems to account for the decreased sensitivity to TRAIL-induced apoptosis [51]. However, later on, additional targets of miR-221/222 – *PTEN/TIMP3* [52] and *PUMA* [53] - were also suggested to mediate TRAIL resistance, consistent with frequent overexpression of miR-221/222 in epithelial cancers [54-56]. MiR-221/222 upregulation is common in more invasive lung cancers, and their functions in lung tumorigenesis involve promotion of invasion through the activation of AKT pathway and metallopeptidases. MiR-221/222 are subjected to activation by MET through c-JUN [52]. Interestingly, miR-130a has been linked to TRAIL-sensitivity regulation by downregulating miR-221/222 via the interaction

with the 3′UTR of *MET* [57]. Besides *MET*, miR-221/222 are also positively regulated by *EGFR* and could decrease sensitivity of lung cancer cells to gefitinib-induced apoptosis by targeting the apoptotic peptidase activating factor 1 (*APAF-1*) [58].

1.4 Other miRNAs that promote lung tumorigenesis

Liu et al. [59] reported that in human bronchial epithelial cells transformed by chemical carcinogen anti-Benzo-A-Pyrene-Diol-Epoxide (anti-BPDE), miR-494 was upregulated and thus repressed tumor suppressor *PTEN*. The activities of caspase-3/7 were also decreased due to the alteration in miR-494 level, suggesting miR-494 as an oncomiR by repressing apoptosis of cancer cells. MiR-27a was found activated in SV40 small T antigen transformed bronchial epithelial cells, and downregulation of miR-27a in such cells decreased the ability of cells to grow in an anchorage-independent manner. MiR-27a overexpression promotes cell growth by suppression of the target gene *FBXW7* which contributes to the malignant transformation of the primary human bronchial epithelial cells [60]. MiR-328 expression level in the lung tumor samples from patients with brain metastases is significantly higher than that from patients without brain metastases. Introduction of miR-328 into A549 cells promoted cell migration comparing to parental A549 cells [61]. MiR-301 is an intronic miRNA hosted in the *SKA2* gene. It can positively regulate expression of its host gene through the ERK/CREB pathway. Inhibition of miR-301 or *SKA2* in A549 cells increased cell proliferation and invasion as reflected by elevated mitotic index and colony formation [62]. The *FUS1* gene is believed to be a TSG based on its frequent expression deficiency in lung cancers and its tumor suppressive activity in mouse model systems [63-65]. Three miRNAs - miR-93, miR-98, and miR-197 - could directly downregulate *FUS1* [66]; these three miRNAs might promote lung cancer growth through repression of *FUS1*. MiR-20, miR-106, and miR-150 were identified as oncomiRs in lung cancer per their activities in regulating A549 cell growth and apoptosis, with miR-106 and miR-150 targeting *RB* and *TP53* respectively [67]. Antisense oligonucleotides against miR-150 reduced volume and weight of established mouse lung tumor xenografts [68]. MiR-30b/c are often downregulated in *MET* or *EGFR*-silenced lung cancer cells [58]. Enforced expression of miR-30b/c would inhibit gefitinib-induced apoptosis by targeting *BIM* [58]. MiR-29a/c and miR-100 exhibit similar activities but the mechanism is not clear [58].

2. Tumor suppressive miRNAs in lung cancer

2.1 let-7 family

Let-7 was one of the early few miRNAs uncovered in *C. elegans* and subsequently was the first miRNA identified in humans [69, 70]. The sequences and functions of this family are well conserved across species. There are 13 members to this family in humans: let-7a-1, 7a-2, 7a-3, 7b, 7c, 7d, 7e, 7f-1, 7f-2, 7g, 7i, miR-98, and miR-202 [71]. Since there are multiple review articles dedicated to let-7s, readers are referred to them for an in-depth discussion [71-76].

2.2 miR-34/449 family

In contrast to let-7 being one of the earliest studied miRNAs, the miR-34/449 family came under spotlight only in recent years. In 2007, several groups reported the connections between miRNAs and the p53 network: miR-34a and miR-34b/c were found to be under direct regulation of p53 to control apoptosis and cell cycle arrest in cancer cell lines [77-80]. MiR-34a and miR-34b/c are homologues and belong to the same family. Another miRNA family discovered later, miR-449a, 449b and 449c together abbreviated as miR-449, share identical seed sequence and secondary structures with miR-34 and therefore was assigned as part of the miR-34 family [81]. MiR-34/449 form a feedback network with p53 and E2F

transcription factors [81]. P53 activates miR-34 while E2F activates miR-449. Both miRNAs directly suppress *E2F* but upregulate p53 by targeting dyacetylase gene *SIRT1*. We categorize the pleiotropic activities of these miRNAs into these classes: (a) arresting cell cycle by targeting *CCND1*, *CCNE2*, *CDC25A*, *CDK4*, *CDK6*, *c-MYC*, *E2Fs*, and *MET*; (b) conferring apoptosis by targeting *BCL-2*, *GMNN*, *N-MYC*, *HDAC1*, *SIRT1* and *MET*; (c) activating senescence by repression of *c-MYC*, *HDMX*, and *SIRT1*; (d) inhibiting cancer cell migration/invasion by repression of *HMGA2*, *AXL*, *SNAIL1*, and *SERPINE1* [81-84].

Several reports have linked miR-34 to lung cancers. In one of the early papers on miR-34 and p53 [85], researchers showed that miR-34b/c expression was significantly reduced in 6/14 (43%) NSCLC samples and restoration of miR-34 inhibited lung cancer cell growth. Greatly reduced expression of miR-34 was found in rat lungs exposed to a chemical carcinogen (nicotine-derived nitrosamine ketone (NNK)) or cigarette smoke [86, 87], in line with the tumor suppressive role of miR-34. MiR-34a and miR-15/16 synergistically induced cell cycle arrest in NSCLC cells in a RB-dependent manner [88]. *AXL* [83] and *SNAIL1* [82] as miR-34 direct targets were identified in lung cancer cells. MiR-34 expression would inhibit lung cancer cell migration and invasion via repression of these genes. Interestingly, a very recent study of miR-34 and SNAIL in colon cancer cells found that SNAIL actually directly repressed miR-34, forming a double negative feedback loop [89]. Pulmonary tissue is a site where miR-449 is preferentially expressed (the other site is testis) [90]. But the literatures about miR-449 and lung cancer are limited. One study detected reduced expression of miR-449a/b in lung cancer tissues compared with matched normal tissues [91]. *HDAC1* was realized as a target of miR-449a/b in lung cancer cells [91]. Ectopic expression o f m i R-449a/b decreased cell viability in multiple lung cancer cell lines and anchorage-independent growth of H1299 cells. Combination of either miR-449a or miR-449b with HDAC1 inhibitor elicited stronger growth inhibition than the inhibitor mono-treatment. Another group reported that introduction of miR-449a/b into H1299 cells induced apoptosis [92]. All these results confirmed that miR-34/449 family acts as tumor suppressors in lung cancers.

2.3 miR-15/16

MiR-15a and miR-16-1 are located at 13q14.3 and were the first miRNAs implicated in oncogenesis. They were found to be frequently deleted or downregulated in chronic lymphocytic leukemia (CLL) in 2002 [13], suggesting their role as tumor suppressors. Gene targets of this cluster include *BCL-2*, *CDC2*, *CCND1*, *ETS1*, *JUN*, *MCL1*, *MSH2*, *PDCD4*, *PDCD6IP*, *RAB9B*, *WT1*, and *WNT3A*, through which this miRNA cluster regulates multiple aspects of tumorigenesis, including cell survival, proliferation and invasion (reviewed in Ref. [93]). Other targets of this cluster were identified along the line of their tumor suppressor functions. MiR-15a and miR-16-1 together with miR-15b and miR-16-2 were identified as direct targets of E2F1 and controls E2F-dependent cell proliferation by targeting *CCNE1* [94]. Fibroblast growth factor 2 (*FGF-2*) and its receptor *FGFR1* were identified as novel targets which affect both stromal cells and prostate cancer cells to promote cancer cell proliferation and invasion [95]. In lung cancers, the miR-15/16 cluster was also frequently deleted or downregulated as in other types of cancers [96]. In NSCLC cell lines, the expression level of the miR-15/16 cluster was inversely correlated with expression level of Cyclin D1. *Cyclins D1*, *D2* and *E1* are directly regulated by these miRNAs in lung cancer cells and overexpression of the miR-15/16 cluster induced G1 arrest in an RB-dependent manner. When combined with miR-34a, the induction of G1 arrest was more profound than the additive effect of treating cells with the two miRNAs separately [88], indicating a cooperation between the two tumor suppressive miRNA clusters.

2.4 miR-200 family and miR-205

The miR-200 family has five members: miR-200a, miR-200b, miR-429, miR-200c, and miR-141. In humans, the first three miRNAs co-localize at chromosome 1 and the latter two co-localize at chromosome 12 [97]. This family together with miR-205 inhibited epithelial-mesenchymal transition (EMT) through targeting *ZEB1* and *ZEB2* [97], highlighting their significance in the regulation of cancer pathogenesis especially with regard to invasion and metastasis. In lung cancers, miR-200c overexpression reduced ZEB1 expression and derepressed the transcriptional target of ZEB1, *E-cadherin,* in A549 cells [98]. Murine model systems revealed that forced expression of the miR-200 family in metastasis-prone mouse lung tumor cells blocked the capability of these cells to go through EMT, thus weakening cellular invasive and metastatic potentials with concomitant alterations in the expression profiles of epithelial and mesenchymal cell marker genes [99]. Expression analysis in 39 human lung cancer cells lines detected strong correlations of miR-141 level with the expression of *CDH1*, *CDH2*, *ZEB1*, *ZEB2*, and *VIM* [99]. In a separate study [100], miR-200c expression was shown to be negatively correlated with invasion in a panel of 9 NSCLC cell lines and ectopic expression of miR-200c in highly invasive cells inhibited mesenchymal phenotypes and *in vivo* metastasis formation. MiR-200b prevented malignant transformation of human bronchial epithelial cells induced by the chemical carcinogen arsenic [101].

Further studies revealed targets beyond *ZEB1* and *ZEB2* that mediate miR-200s/miR-205-dependent regulation of EMT and metastasis in lung cancers. The Kurie group utilized bioinformatics tools to search for targets of miR-200s, and validated one of the 35 predicted targets [102]: *Flt1* in a mouse lung cancer system. They later identified *GATA3*, a component of the Notch signaling pathway, as downregulated by miR-200s [103]. In a luciferase reporter assay, although *GATA3* 3′UTR was inhibited by miR-200s to a statistically significant level, the level of inhibition was not as profound as seen with the *ZEB1* 3′UTR. Thus, *GATA3* may be an indirect target of miR-200s. To expand their efforts in elucidating miR-200 targets in the EMT regulation pathway, they harnessed a proteomics approach to compare expression profiles of lung cancer cells with or without miR-200s restoration [104]. Over 300 proteins showed changed expression, which can be categorized as peptidases, cell adhesion andextracellular matrix (ECM) proteins and cytoskeletal regulators. Surprisingly, Korpal et al. discovered that miR-200s promote metastatic colonization to the lung by direct targeting *Sec23a* [105]. The miR-200 family also regulates multidrug sensitivity in lung cancers [106]. MiR-200b/c and miR-429 were down-regulated in multidrug resistant cells and restoration of this cluster sensitized cells to anti-cancer drugs. The regulation of drug-induced apoptosis is through targeted inhibition of anti-apoptotic factors *BCL-2* and *XIAP*.

2.5 miR-143/145

MiR-143 and miR-145 are co-transcribed from a bicistronic gene cluster on chromosome 5 [107]. They have been identified as tumor suppressors in multiple cancers such as colorectal cancer, bladder cancer, gastric cancer, cervical cancer, breast cancer, prostate cancer and leukemia [108-114]. In an analysis of miRNA expression patterns in the rodent lung exposed to carcinogenic cigarette smoke [86], miR-145 was one of the severely downregulated miRNAs, connecting this miRNA to lung carcinogenesis. Soon after that, the inhibitory effect of miR-145 on cell growth was reported in mouse lung cancer cells [115] and confirmed in humans [116]. *C-MYC*, *EGFR*, *NUDT1*, and *OCT4* were all identified as targets and mediators of miR-145 for cell proliferation regulation in lung cancers [117-119]. Besides cell growth, miR-145 regulates cell cycle and causes G1 arrest by targeting *CDK4* in lung cancers [118]. Inhibition of lung cancer metastasis by miR-145 was observed in an animal model, partly by targeting *MUC1* [120]. Similarly, miR-143 was downregulated in

chemical-induced mouse lung tumors [121], whereas in human lung tumor samples, expression of both miR-145 and miR-143 were reduced comparing to normal tissues [122]. In contrast to miR-145, less is known regarding the involvement of miR-143 in lung tumorigenesis.

2.6 Other miRNAs that suppress lung tumorigenesis

The miR-29 family (miR-29a, b, and c) activates p53 by targeting its negative regulators, *p85α* and *CDC42*. This family has been extensively studied in CLL [123-125]. In the pulmonary tissue, miR-29s are considered important regulatory factors for fibrosis [126]. In lung cancers, expression of miR-29s is inversely correlated to that of the DNA methyltransferases *DNMT3A* and *-3B* [127], both of which are direct targets of miR-29s. The enforced expression of miR-29s in lung cancer cell lines inhibited tumorigenicity *in vitro* and *in vivo* through demethylation and reactivation of epigenetically silenced TSGs such as *FHIT* and *WWOX* [127]. Other important targets that mediate miR-29 function as a tumor suppressor include *TTP* [128] (which regulates cell polarity and metastasis) and the *BCL-2* family member *MCL-1* [129].

MiR-1, miR-133, and miR-206 are three so called “muscle specific” miRNAs highly expressed in cardiac and smooth muscle tissues [130, 131]. They exhibit cancer suppressive activities in the lung. MiR-1 was downregulated in primary lung cancer samples and cell lines [132]. Enforced expression of miR-1 in A549 and H1299 cells inhibited cell growth, replicative potential, motility/migration, clonogenic survival and tumorigenicity in mice [132]. Targets mediating these effects include *MET*, *PIM-1*, *HDAC4*, and *FOXP1*. MiR-133a is expressed at a reduced level in lung squamous cell carcinomas (SqCC) relative to normal tissues [133]. Restoration of miR-133a in lung SqCC cell lines inhibited cell proliferation. Multiple targets were predicted and two of them (*ARPC5* and *GSTP1*) were confirmed in lung cancer cells [133]. Analysis of miR-206 expression in lung tumors and cell lines established that miR-206 level is lower in highly metastatic tumors. Upregulation of miR-206 in cancer cell lines resulted in induction of apoptosis and inhibition of cell proliferation, migration, and invasion [131].

MiR-126 and its complementary species miR-126* are encoded by intron 7 of the *Epidermal Growth Factor-Like Domain 7* (*EGFL7*) gene [134]. MiR-126/126* are important factors for angiogenesis and vascular integrity through repression of inhibitors of vascular epithelial growth factor (VEGF)-induced proliferation (reviewed in [134]). In terms of tumorigenesis, studies so far have assigned them as tumor suppressors. Both miR-126 and miR-126* were downregulated in lung cancers [134-137]. Through targeting *VEGF*, miR-126 decreased lung cancer cell growth, induced cell cycle arrest at G1 phase, and impaired tumorigenicity of mouse-hosted tumor xenografts [138]. By downregulating *CRK* at protein level, miR-126 retarded adhesion, migration, and invasion of NSCLC cells [139, 140]. MiR-126 also promoted irradiation-induced apoptosis in NSCLC cells [137]. In SCLC cells, miR-126 slowed down cellular proliferation via targeting *SLC7A5* [141]. It is known that miR-126 negatively regulates its host gene *EGFL7* and this feed-back signaling manifests itself in lung tumorigenesis both *in vitro* and *in vivo* [142].

Frequent loss of heterozygosity (LOH) for miR-128b located on chromosome 3p was discovered in NSCLC samples [143]. *EGFR* was realized as a direct target for this miRNA [143]. Thus, a reduction in miR-128 expression would promote carcinogenesis via derepression of an oncogene (i.e, *EGFR*). MiR-142-5p was suppressed in mouse and human lung cancers, and transfection of miR-142-5p significantly suppressed lung cancer growth [115]. Expression of miR-451 was reduced in human lung cancer samples and ectopic expression of this miRNA significantly inhibited NSCLC cell proliferation and colony formation as well as xenograft tumor growth in nude mice by inducing apoptosis [144].

RAB14 was a confirmed target mediating this effect [144]. A reduced level of miR-101 was seen in human lung cancers and correlated with the overexpression of either one of the two targets: *EZH2* [145] or *MCL-1* [146]. Introduction of miR-101 into NSCLC cells decreased cell proliferation, invasion and sensitivity to drug-induced apoptosis [145]. MiR-218 negatively impacted NSCLC cell proliferation, invasion and soft agar colony formation by repressing *PXN* [147]. MiR-129 repressed cell cycle progression thus cell growth of lung adenocarcinoma (AD) cells by targeting *CDK6* [148]. MiR-212 induced apoptosis of NSCLC cells by targeting an antiapoptotic protein PED [149]. Since miR-519c negatively regulates the expression of HIF-1α [150] (a key factor for tumor angiogenesis [151]), this miRNA inhibits angiogenesis of lung cancers [150]. The cancer prevention activity of the green tea polyphenol epigallocatechin-3 gallate (EGCG) is believed to be partially mediated by miR-210 [152]. Two miRNAs under negative regulation of the *MET* oncogene, miR-103 and miR-203, were shown to promote gefitinib-induced apoptosis through inhibition of protein kinase C ε (PKC-ε) and sarcoma viral oncogene homolog (SRC), respectively [58].

3. miRNAs that exhibit both pro- and anti-lung cancer functions

As in protein-coding genes, individual miRNAs may exhibit both pro- and anti-cancer activities in a context-dependent manner. Below, we discuss selected cases with relevance to lung cancers.

3.1 miR-7

In the human genome, there are three miR-7 host genes on chromosome 9, 15, and 19, respectively. The function of this miRNA was first studied in *Drosophila* [153]. In 2008, it was identified as a tumor suppressor in glioblastomas [154], directly targeting *EGFR* as well as downregulating the AKT pathway to decrease viability and invasiveness of cancer cells. This effect was confirmed in the A549 lung cancer cells a year later [155]. Moreover, miR-7 was also reported to inhibit A549 cell growth by targeting *BCL-2* [156]. On the other hand, Chou et al. reported miR-7 as an oncomiR in lung cancers [157]. They detected an elevated miR-7 expression in human lung cancers and a significant correlation between EGFR and miR-7 expression in *EGFR* mutated but not in *EGFR*-wild-type lung cancers. EGFR can induce miR-7 expression through the RAS/ERK/MYC pathway. Enforced expression of miR-7 promoted proliferation and tumorigenicity of CL1-5 lung cancer cells by targeting Ets2 transcriptional repressor (*ERF*) [157].

3.2 miR-31

The host gene encoding hsa-miR-31 is at chromosome 9. The expression of miR-31 in the lung can be induced by chemical carcinogens like cigarette smoke or vinyl carbamate [121, 158]. MiR-31 is also overexpressed in both mouse and human lung cancers [158, 159]. Gain- and loss-of-function experiments established the role of miR-31 on enhancing proliferation and tumorigenicity of lung cancer cells [158, 159]. Two TSGs are targets of miR-31: *LAST2* and *PPP2R2A* [159]. On the contrary, in established pulmonary metastasis of breast cancer, miR-31 would trigger regression of the metastasis by targeting *ITGA5*, *RDX*, and *RhoA* [160, 161], playing a metastasis suppressor role.

3.3 miR-125

The miR-125 family includes two members with identical seed sequence: miR-125a transcribed from a gene at chromosome 19, and miR-125b encoded by two separate genes at chromosome 11 and 21 respectively. In 2007, both microRNAs were identified as tumor suppressors in breast cancer through downregulation of *ERBB2* and *ERBB3* genes [162]. Their tumor suppressive functions were also confirmed in other cancers like glioblastoma [163] and gastric cancer [164]. Perplexingly, miR-125a/b also target *TP53*, suggesting their

roles as oncomiRs [165, 166]. In lung cancers, genes encoding miR-125b were frequently deleted [167, 168]. MiR-125a-3p, a newly identified derivative of miR-125a, has an opposing function to miR-125a-5p (previously miR-125a). A reduced expression of miR-125a-3p was reported in NSCLC tissues [169] and in lung cancers cells with higher metastatic potential [170]. The role of miR-125a-3p in inhibiting lung cancer invasion and metastasis was confirmed by both loss- and gain-of-function experiments [169]. As to miR-125a-5p, findings so far have been inconclusive as miR-125a-5p has been found to be capable of inhibiting [171] or promoting [169, 172] metastasis.

3.4 miR-183-96-182

Human miR-183 family members (miR-183, miR-182, and miR-96) are co-expressed from an intergenic region on chromosome 7. They have both common and distinctive targets. All three members repress zinc transporters that regulate zinc homeostasis in cancers [173]. *FOXO1* is another common target [173]. Distinctive targets for different family members include: *EZRIN*, *ITGB1*, *KIF2A*, *PDCD4*, and *EGR1* for miR-183 [174-177]; *KRAS* for miR-96 [178]; *RGS17*, *BRCA1*, and *CTTN* for miR-182 [179-181]; *FOXO3* for miR-96 and miR-182 [182, 183]. MiRNAs in this family regulate the development of multiple cancer types like breast cancer [184-187], colorectal cancer [188, 189], hepatocellular carcinoma [175], endometrial cancer [173], pancreatic cancer [178, 190], ovarian cancer [191], and bladder urothelial carcinoma [192], etc. All three members have been shown to have both oncogenic and tumor suppressive functions. In lung cancers, overexpression of the miR-183 family was identified as a risk factor [193]. But miR-183 was also demonstrated to inhibit lung tumor invasion and metastasis through targeting *EZRIN* [177]. Likewise, a similar scenario with invasion and metastasis has been reported for miR-182 and its target *CTTN* [181]. MiR-182 inhibited lung cancer cell proliferation and anchorage-independent growth by suppression of *RGS17* [180]. Research for specific targets and functions of miR-96 has not been conducted in lung cancers. In view of the evidence that the miR-183 family keeps invasion and metastasis in check [177], the positive correlation of miR-183 overexpression with lung cancer risk may indicate an oncogenic role for miR-183 in other aspects of tumorigenesis, such as cell death control or angiogenesis.

4. miRNAs and lung developmental genes

Thyroid transcription factor 1 (*TTF-1* or *NKX2-1*) is a member of the NKX family transcription factors characterized by the DNA binding homeodomain [194]. The expression of TTF-1 is largely restricted to lung, thyroid, and forebrain [195]. The role of TTF-1 in lung development and morphogenesis has been well established [196]. *Ttf-1* null mice were born dead and lacked lung parenchyma [195]. Genetically engineered mice expressing a mutant form of TTF-1 resistant to phosphorylation at seven serine residues die immediately after birth. Although lobulation and branching morphogenesis were maintained, the mutant animals displayed pulmonary hypoplasia and abnormalities in acinar tubules [197]. These reports explicitly identified TTF-1 as a master regulator of lung development. In 2007, TTF-1 amplification in lung cancers was reported by us and others [198-201], with gain- and loss-of-function studies in cell systems suggesting *TTF-1* as a lineage specific oncogene. But the subsequent reports of TTF-1 suppressing lung cancer development in a mouse model [202] and TTF-1 counteracting TGF-β-induced EMT in lung cancer cells [203] complicate this issue. Despite the complexity, the study about molecular mechanisms of *TTF-1* regulation is warranted. To this end, our laboratory utilized a candidate-based approach to search for miRNAs that regulate TTF-1 [204]. We were able to validate one miRNA (miR-365) out of the ten candidates predicted by TargetScan algorithm [205]. MiR-365 is encoded by two genes located at chromosome 16 and 17. Both genes repressed the *TTF-1* 3′UTR reporter and reduced endogenous TTF-1 protein expression when transduced into lung cancer cells. TGF-β repression of TTF-1 seemed to be at least partially mediated by

inducing miR-365. This miRNA also upregulates TGF-β2 to form a signaling loop [204]. These observations have opened up a new and miRNA-based angle to examine the biology of TTF-1. Achaete-scute homologue-1 (*ASH1*) is a basic helix–loop–helix transcription factor important for the development of neuroendocrine (NE) features in normal lung cells as well as lung cancer cells. Newborn mice with a disrupted *ASH1* gene had no detectable pulmonary NE cells. Knockdown of *ASH1* in lung cancer cells with NE features repressed expression of the NE markers [206]. Lung cancer cells with NE features are often very aggressive, and ASH1 was shown to promote airway dysplasia and tumorigenicity of SV40 large T antigen in the airway epithelium [207]. This suggests that ASH1 is more than a mediator for the induction of NE features in the lung. Recently, miR-375 was identified as a transcriptional target of ASH1. This microRNA was normally coexpressed with *ASH1* in a lineage–dependent manner, and alleviated the growth inhibitory effect in lung cancers imposed by the miR-375 target gene *YAP1*, thus mediating tumor promoting activity of ASH1 [208].

5. Clinical implications

The intertwined network of miRNAs, oncogenes, TSGs, and lung developmental genes implicates ubiquitous involvement of miRNAs in all aspects of lung cancer pathogenesis. This raises the possibility of developing novel methods for lung cancer interventions, including diagnosis, risk evaluation, outcome prediction, or treatment using miRNAs.

5.1 miRNAs for lung cancer diagnosis

In 2006, high expression of let-7a-2 and low expression of miR-155 were used to discriminate lung cancer tissues from noncancerous lung tissue [209]. Later, circulating miRNAs in the blood plasma and serum were found to be stable [210]; and an elevated expression of miR-25 and miR-223 was identified as a biomarker for NSCLC. This finding paved the way for noninvasive diagnosis of lung cancers using blood-miRNA expression patterns. Following that, extensive studies gave rise to a burst of different “miRNA signatures” for lung cancer diagnosis. For example, simultaneous overexpression of miR-155, miR-182, and miR-197 discriminated lung cancers from cancer-free controls with 81.33% sensitivity and 86.76% specificity in a cohort of 74 patients and 68 matched controls [211]. Diagnosis of NSCLC based on elevated levels of serum miR-1254 and miR-574-5p showed over 70% sensitivity and specificity in two separate cohorts [212]. Boeri et al. [213] generated a plasma-derived signature consisting of 16 miRNA expression ratios from 13 miRNAs for lung cancer diagnosis with >80% sensitivity and specificity. Moreover, they reported a 15-miRNA signature predictive for lung cancer development in disease-free smokers, which might be even more helpful for early detection of disease.

Sputum as a unique type of body fluid in lung cancer diagnosis has been found to contain miRNAs that can also serve as a biomarker for lung cancer detection. From sputum samples, the Jiang group found that overexpression of miR-21 clearly discriminated NSCLC patients from cancer-free individuals [214]. Overexpression of miR-21, miR-200b, and miR-375 combined with a reduced level of miR-486 segregated AD patients from normal individual with 80.6% sensitivity and 91.7% specificity [214], while downregulation of three miRNAs (miR-205, miR-210, and miR-708) predicted SqCC with 73% sensitivity and 96% specificity [214]. Another miRNA signature, based on the expressions of 34 miRNAs, detected early-stage NSCLC in asymptomatic individuals with 80% accuracy [215].

Besides discriminating cancer from normal status, miRNAs can also help classify lung cancer subtypes. A miRNA expression study in 165 AD and 125 SqCC tissues led to 127 miRs with significant differential expression between AD and SqCC groups [216]. In another study with 60 SqCC patients and 62 AD patients, miR-205 was identified as a

highly specific marker of SqCC, and the expression ratio of miR-205/miR-21 can differentiate SqCC against AD with over 90% accuracy and sensitivity [217]. The robustness of miR-205 and miR-21 expressions in discriminating AD and SqCC was confirmed in a separate study recently [213]. These miRNA-based diagnostic markers are of promising clinical value since SqCC and AD require different treatments. MiRNAs could also serve as a marker to differentiate primary lung tumors from lung metastases from other sites. Barshack et al. found that miR-182 was most significantly overexpressed in primary lung tumors while miR-126 was overexpressed in lung metastases in two separate sets of samples tested [218].

A factor that impedes the translation of laboratory-derived miRNA expression signatures into clinics is the lack of reproducibility [219]. This could be partly explained by discrepancies in microarray platforms, experimental operations, analysis methods, and sample properties (e.g., ethnicity of patients). Moreover, miRNA signatures in lung cancers change with disease progression [220]. But more importantly, the small number of samples analyzed in most of the profiling studies and the correlated data structure contributed to a large part of the signature instability [219]. To develop better miRNA biomarkers for clinical use, a much larger sample size and a standard operating protocol with standardized platforms and data analysis methods are essential. Markers developed in such a manner are likely to have a higher success rate for clinical adaptation.

5.2 miRNAs for lung cancer prognosis

In the first report bringing miRNAs into the lung cancer research field, a low level of let-7 expression was found to be significantly associated with poor survival in surgically-resected NSCLC patients [221], suggesting a prognostic value for miRNAs. This was corroborated by a large number of subsequent studies. The prognostic value of let-7 was initially confirmed [209] but later refuted in a set of 51 AD samples [222]. The correlation of high miR-21 level, in tumors or sera, with poor survival of lung cancer patients, was reported by several groups independently [122, 134, 223-227]. Lower expression of individual miRNAs other than let-7 predicted poor survival or high recurrence of lung cancers. These miRNAs include miR-34a [228], miR-374a [229], miR-181a [122], miR-221 [230], miR-200c [223], and miR-218 [147]. On the other hand, some miRNAs showed the opposite predictive trend (similar to miR-21). MiRNAs in this latter group include the miR-183 family (miR-182, miR-183, and miR-96) [193], miR-31 [188], miR-16 [231], miR-92a-2* [232], and miR-126 [233]. The correlation of high miR-126 level with poor prognosis is especially significant in the SqCC subtype. Also, a high level of miR-126 was correlated with increased VEGF in the tumor, and co-expression of miR-126 and VEGF had a significant diagnostic impact for poor survival. The diagnostic value for miR-155 is still ambiguous. An initial study correlated high level of miR-155 with poor prognosis [209], whereas a later report showed that miR-155 level was a negative predictor for AD, but a positive one for SqCC with lymph node metastases. If not divided by subtype, the overall patient survival in the second study was not associated with the level of miR-155 [234]. For SqCC, miR-146b alone was found to have the prediction accuracy for stratifying prognostic groups at 78% [235].

Several other signatures are based on the combined expression levels of multiple miRNAs. A high level of miR-486 and miR-30d combined with a low level of miR-1 and miR-499 in the serum could significantly predict poor survival for NSCLC [236]. And a five-miRNA signature (miR-25, miR-34a, miR-34c-5p, miR-191, and let-7e) was reported by the Wang group to predict survival for SqCC subtype specifically [216]. A plasma signature of 9 miRNAs in pre-disease samples of lung cancer patients reliably predicts the risk of aggressive development of the disease with poor prognosis [213]. Interestingly, the samples collected from the same cohort at the time of disease detection revealed a different miRNA signature for prognosis. A common feature shared by the two signatures was the

downregulation of miR-486-5p [213]. This finding supports the notion that miRNA signature evolves with disease progression.

Besides miRNA level, changes in methylation status of miRNAs could independently predict lung cancer prognosis [237]. Methylation of miR-9-3 and miR-124-2/3 is individually correlated with advanced T stage of lung cancer, and a higher number of overall methylation sites is correlated with poor survival [238]. Methylation of miR-34b/c is independently correlated with high recurrence and poor overall survival (OS) for stage I NSCLC [237]. The expression levels of miRNAs could also serve as indicators for drug responses in lung cancers. For example, Ranade et al. reported that high levels of miR-92a-2*, miR-147, and miR-547-5p were correlated with chemoresistance in SCLC patients [232]. The inconsistency of reported miRNA-based biomarkers is a similar issue in prognosis as it is in diagnosis. Efforts towards solving this problem would hopefully clear up the controversies surrounding a selection of miRNAs and further increase the prognostic values of miRNAs as a group for lung cancers.

5.3 miRNAs polymorphisms, lung cancer susceptibility and prognosis

New findings in recent years have demonstrated that expression and functions of miRNAs can be altered by sequence polymorphisms in the miRNA genes, miRNA processing machinery genes or miRNA target genes [239, 240]. Emerging evidences suggest that certain miRNA polymorphisms may be indicators for cancer predispositions and outcome [240, 241]. The single nucleotide polymorphism (SNP) rs11614913 T>C in hsa-mir-196a2 (the precursor for miR-196) enhanced miRNA processing to produce more mature miRNA, resulting in an enhanced binding of miR-196a to its targets [242]. The CC genotype correlated with both heightened susceptibility to lung cancers and decreased survival in NSCLC patients in Chinese population [242, 243].

Among the miRNA processing machinery genes, three harbor SNPs associated with lung cancer risk or prognosis. In a case control study, the rs636832A>G SNP in *AGO1* was associated with decreased lung cancer risk in a dose-dependent manner [244]. Moreover, a haplotype (defined as a combination of alleles) in *Drosha* (GTAATC), was associated with a reduced survival of lung cancer patients, and the rs640831G>T SNP included in this haplotype is correlated with expression changes of cancer-related miRNAs such as let-7s and miR-21 in AD patients [245]. In another miRNA machinery gene *XPO5*, AA genotype for the rs11077A>C SNP was independently associated with time to relapse (TTR) in surgically-resected stage-I NSCLC patients [246].

SNPs that affect miRNA-based regulation of the target genes and consequently lung cancer risk and prognosis were detected in four genes so far. One SNP in the let-7 binding site within *KRAS* 3′UTR, termed LCS6, influenced KRAS expression level and was correlated with increased lung cancer risks in moderate smokers, but not *KRAS* mutation or lung cancer survival [247, 248]. The CC genotype in *KRT81* SNP rs3660C>G, is associated with TTR in surgically-resected NSCLC patients, especially in SqCC patients [246]. Since this SNP would alter the binding sites of these miRNAs - miR-17, miR-93, miR-20b, miR-519d, miR-520g, miR-520h, miR-519c-3p, miR-519b-3p, miR-519a, and miR-765 - the target-binding alteration in one or more of these miRNAs may be the basis of the differential prognosis. The *MYCL1* oncogene contains the rs3134615G>T SNP within the miR-1827 binding site. This SNP alleviates *MYCL1* repression by miR-1827 and increases susceptibility to SCLC [249]. An increased risk of lung cancers can also be associated with the CC genotype in the rs2735383G>C SNP of the *NBS1* gene. This is mediated by an altered interaction of *NBS1* with miR-629, resulting in a reduced level of NBS1 expression in the CC genotype carriers [250].

5.4 miRNA based therapies for lung cancer

Given the significant roles that miRNAs play in multiple pathways of lung carcinogenesis, increasing efforts are dedicated to research and development of miRNA-based therapies, including restoring functions of tumor suppressive miRNAs ("miRNA replacement therapy [251]") or inhibiting oncogenic miRNAs.

Exogenous delivery of let-7 into mouse models of lung cancers significantly reduced tumor growth or decreased tumor burden in established tumors, implying that miRNA replacement therapy could be promising [252-254]. Also, liposome-based delivery of miR-7 into mouse xenografts of human lung tumors resulted in significant shrinking of the tumors [255]. Activation of miR-31 function diminished tumor burden in established macroscopic pulmonary metastasis of breast cancers. MiR-34a based strategy has been proved effective in mouse lung cancer models by two separate groups [256, 257]. Comparing to siRNA based therapies which are already in clinical trials, miRNAs are less toxic [258] and capable of "multi-targeting", pointing to their potential to enter clinical practices. The critical issues for the development of this therapy are fast and effective delivery into target sites, potency of the therapy, and elimination of off-target effects. Towards solving these issues, double-stranded miRNA mimics promise an easier and cost-effective source of functional mature miRNAs with less non-specific effects comparing to miRNA-expressing viral vectors or chemically synthesized pre-miRs. Let-7 double-stranded mimics were tested in lung cancer cell lines for the inhibition of tumorigenic properties and were proven effective [259]. Lipid- and nanoparticle-based delivery systems were demonstrated to execute effective delivery to lung cancer cells or to animals locally and/or systematically [256-259]. Chemical modifications at the 3′-end of let-7 double-stranded mimics may increase the activity of the mimic [259].

To achieve therapeutic effect through targeting oncomiRs, several types of miRNA inhibitors have been developed. Chemical modifications, like 2′-O methyl and Locked Nucleic Acid (LNA), would increase oligo stability against nucleases. Antisense oligonucleotides with these modifications are termed "antagomirs" and "LNA-antimiRs", respectively [260, 261]. A new class of miRNA inhibitors, "miRNA sponges", can be expressed in cells from transgenes of tandem miRNA binding sites linked to a strong promoter [262]. A LNA-antimiR against miR-122 has been shown to effectively silence miR-122 in primates without evidence for toxicity, suggesting the feasibility of miRNA inhibitors for utilization in clinical settings [261]. In lung cancers, anti-miR-150 delivered intratumorally into lung tumor xenografts in mice led to tumor regression in volume and weight [68]. To inhibit families of miRNAs sharing identical seed sequences, seed-targeting 8-mer LNAs (termed "tiny LNAs") have been developed [263], affording a tool to selectively inhibit miRNAs at the basis of individual families.

Resistance to chemo- or radio-therapy is a roadblock for the current treatment of lung cancers. Many miRNAs have been shown to alter responses of lung cancer cells to different drugs or irradiation. MiRNAs reported to alter lung cancer responses to chemotherapy drugs are summarized in Table 1. Let-7a and let-7b were shown to radiosensitize lung cancer cell A549, and probably so do other members of the let-7 family except let-7g based on the expression pattern changes after irradiation [264]. Let-7g was shown to be radioprotective for lung cancer cells in one study [264] but radiosensitizing in two others [265, 266]. More research is needed to solve this myth. Another miRNA reported to radiosensitize lung cancer cells was miR-26b [267], whereas miR-155 [268], miR-9 [265, 269], miR-7 [269], and miR-126 [136] had the opposite effect. In these situations, combining miRNA mimics or inhibitors with traditional therapies may potentiate the efficacy of the treatment. Overall, miRNA-based therapies, alone or in combination with conventional therapies, are still in its infancy; yet, its potential is promising. Inspiringly, a clinical trial in NSCLC using a let-7a-1

based therapy has been initiated [270]. Future efforts should focus on chemical modifications and delivery of the miRNAs, especially targeted delivery to tumor sites without harming non-cancer cells.

6. Conclusions

Evidently, miRNAs are not only regulators for many cancer related genes, but also targets of important oncogenes or TSGs, like *RAS* or *TP53*. Moreover, each miRNA can target several cancer pathways while key factors in the cancer network are usually under heavy posttranscriptional regulation by multiple miRNAs. Through the interwoven web, miRNAs regulate a number of hallmark processes of tumorigenesis like cell growth, proliferation, invasion, and angiogenesis, acting as oncomiRs, tumor suppressors, or players of varying functions depending on the cellular context (Fig. 1). Better methods to systematically identify targets for miRNA(s) or miRNA regulators for genes of interest would produce a more complete understanding of functions of miRNAs in the signal transduction cascades of critical cancer genes. The involvement of miRNAs in cancer pathogenesis provides novel opportunities for cancer interventions. MiRNAs as biomarkers for lung cancer diagnosis, classification, diagnosis, and drug response evaluation is promising but in need of further improvement. Expression analysis in larger cohorts with standardized operational and analysis procedures are likely to generate more robust markers with enhanced sensitivity and specificity. Development of therapies based on miRNAs is still a young field but growing prosperously with the help of new delivery technologies like nanoparticles. Overall, we are optimistic that miRNA-based management of lung cancers will help tame the “Devil” in the future.

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Abbreviations

ACS	American Cancer Society
AD	adenocarcinoma
AGO1	Argonaute-1
AKT	v-akt murine thymoma viral oncogene homolog
Apaf1	apoptotic peptidase activating factor 1
ARPC5	actin related protein 2/3 complex, subunit 5
ASH1	achaete-scute homologue-1
AXL	AXL receptor tyrosine kinase
BCL-2	B-cell CLL/lymphoma 2
BIM	BCL2-like 11
BPDE	Benzo-A-Pyrene-Diol-Epoxide
BRCA1	breast cancer 1, early onset
Btg2	BTG family, member 2
CCND1	cyclin D1
CCNE2	cyclin E2

CDC2	cyclin-dependent kinase 1
CDC25A	cell division cycle 25 homolog A
CDC42	cell division cycle 42
CDH1	E-cadherin
CDH2	N-cadherin
CDK4	cyclin-dependent kinase 4
CDK6	cyclin-dependent kinase 6
c-JUN	V-jun avian sarcoma virus 17 oncogene homolog
CLL	chronic lymphocytic leukemia
c-MYC	v-myc myelocytomatosis viral oncogene homolog
CRK	v-crk sarcoma virus CT10 oncogene homolog
CTGF	connective tissue growth factor
CTTN	cortactin
DGCR8	DiGeorge syndrome critical region gene 8
Dicer	dicer 1, ribonuclease type III
DMC	demethylcantharidin
DNMT3A	DNA (cytosine-5-)-methyltransferase 3 alpha
Drosha	drosha ribonuclease type III
E2F	E2F transcription factor 1
ECM	extracellular matrix
EGCG	epigallocatechin-3 gallate
EGFL7	Epidermal Growth Factor-Like Domain 7
EGFR	epidermal growth factor receptor
EGFR-TKI	EGFR tyrosine kinase inhibitors
EGR1	early growth response 1
EMT	epithelial-mesenchymal transition
ERBB2/3	v-erb-b2 erythroblastic leukemia viral oncogene homolog 2/3
ERF	Ets2 transcriptional repressor
ETS1	v-ets erythroblastosis virus E26 oncogene homolog 1
EZH2	enhancer of zeste homolog 2
Faslg	Fas ligand (TNF superfamily, member 6)
FBXW7	F-box and WD repeat domain containing 7
FGF-2	fibroblast growth factor 2
FGFR1	FGF-2 receptor
FHIT	fragile histidine triad gene
Flt1	fms-related tyrosine kinase 1

FOXO1	forkhead box O1
FOXP1	forkhead box P1
FUS1	fused in sarcoma
GATA3	GATA binding protein 3
GMNN	geminin, DNA replication inhibitor
GSTP1	glutathione S-transferase pi 1
HDAC1/4	histone deacetylase 1/4
HDMX	Mdm2 p53 binding protein homolog
HIF-1α	hypoxia inducible factor 1, alpha subunit
HMGA2	high mobility group AT-hook 2
IL-6	interleukin 6
ITGA5	integrin, alpha 5
ITGB1	integrin, beta 1
KIF2A	kinesin heavy chain member 2A
Kit	v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog
KRT81	keratin 81
LNA	Locked Nucleic Acid
LOH	loss of heterozygosity
MASPRIN	serpin peptidase inhibitor, clade B (ovalbumin), member 5
MCL1	myeloid cell leukemia sequence 1
MET	met proto-oncogene
miRNA	microRNA
MSH2	mutS homolog 2
MUC1	mucin 1
NBS1	nijmegen breakage syndrome 1
NE	neuroendocrine
NKX2-1	see TTF-1
NNK	nicotine-derived nitrosamine ketone
NSCLC	non-small cell lung cancer
NUDT1	nudix (nucleoside diphosphate linked moiety X)-type motif 1
OCT4	POU class 5 homeobox 1
OS	overall survival
Pdcd4	programmed cell death 4
PDCD6IP	programmed cell death 6 interacting protein
PED	phosphoprotein enriched in astrocytes 15
p-EGFR	phosphorylated EGFR

PI3K	phosphoinositide-3-kinase
PIM-1	pim-1 oncogene (proviral integration site 1)
PKC-ε	protein kinase C ε
PPP2R2A	protein phosphatase 2 regulatory subunit B alpha
PTEN	phosphatase and tensin homolog
PUMA	p53 upregulated modulator of apoptosis
PXN	paxillin
RAB9B	RAB9B member RAS oncogene family
RAB14	RAS-related protein 14
RDX	radixin
RGS17	regulator of G-protein signaling 17
RhoA/B	ras homolog gene family, member A/B
RISC	RNA induced silencing complex
ROS	reactive oxygen species
SCLC	small cell lung cancers
SERPINE1	serpin peptidase inhibitor clade E
SIRT1	sirtuin 1
SLC7A5	solute carrier family 7
SNAIL1	snail homolog 1
SNP	single nucleotide polymorphism
Spry1/2	sprouty homolog 1/2
SqCC	squamous cell carcinomas
SRC	sarcoma viral oncogene homolog
TGF-β	Transforming growth factor beta
TGFBR2	transforming growth factor, beta receptor II
TIMP3	TIMP metallopeptidase inhibitor 3
TNF	tumor necrosis factor
TP53	p53 tumor suppressor
TPM1	tropomyosin 1 (alpha)
TRAIL	Apo2L/TNF-α-related apoptosis-inducing ligand
TSG	tumor suppressor gene
TSP1	tumor suppressor region 1
TTF-1	thyroid transcription factor 1
TTR	time to relapse
UTR	untranslated region
VEGF	vascular epithelial growth factor

VIM	vimentin
WNT3A	wingless-type
MMTV integration site family	member 3A
WT1	Wilms tumor 1
WWOX	WW domain containing oxidoreductase
XIAP	X-linked inhibitor of apoptosis
XPO5	exportin 5
YAP1	Yes-associated protein 1
ZEB1/2	zinc finger E-box binding homeobox 1/2

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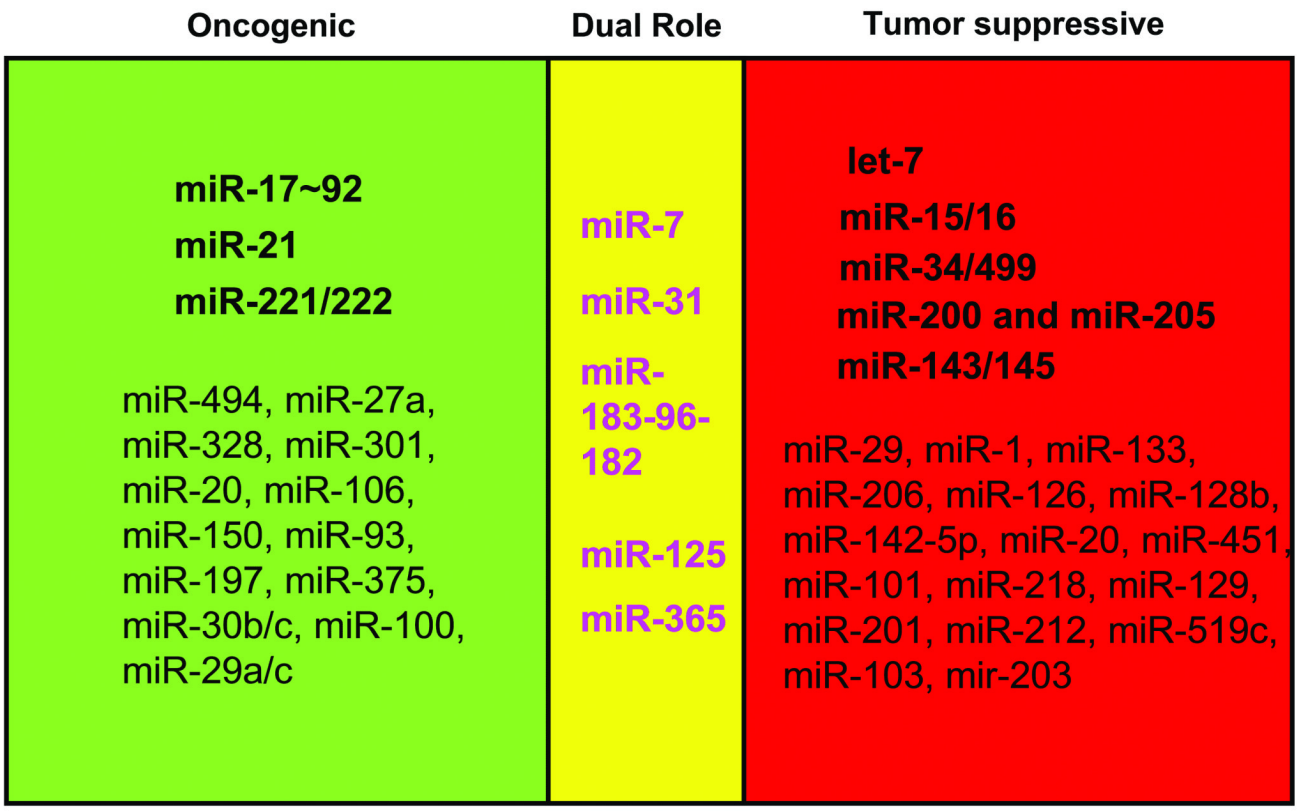

Figure 1. MiRNAs involved in the "Yin" or "Yang" side of lung cancer pathogenesis

"Dual role" indicates those miRNAs that exhibit either pro- or anti-oncogenic activity depending on the biological context.

Table 1

microRNAs experimentally validated to alter chemosensitivity of lung cancers

Drug	MiRNAs Affecting Response to Drug	Sensitivity Change When MiRNA Expressed	References
TRAIL	miR-212,miR-130a	Increase	[57, 149]
	miR-221/222	Decrease	[52]
Cisplatin	miR-181a, miR-181b	Increase	[100, 271-276]
	miR-497, miR-451, miR-138, miR-200c miR-150 miR-134/379/495 miR-630, miR-106	Decrease	[67, 272]
Doxorubicin	miR-1		
	miR-134/379/495	Increase	[132, 273]
Docetaxel	miR-200b,miR-100	Increase	[277, 278]
Cetuximab	miR-200c	Increase	[100]
Etoposide	miR-134/379/495	Increase	[273]
MEK inhibitor			
AZD6244	miR-17	Decrease	[279]
EGFR-TKI			
AG1478	miR-21	Decrease	[36]
Vincristin	miR-181b, miR-497	Increase	[275, 276]
DMC	miR-106, miR-150	Decrease	[67]
Gefitinib	miR-221/222, miR-30b/c	Decrease	[58]
	miR-21, miR-29a/c miR-100 miR-103, miR-203	Increase	[58]

DMC, Demethylcantharidin.