Journal of Cancer Research and Clinical Oncology (2019) 145:31–48
https://doi.org/10.1007/s00432-018-2767-5

REVIEW – CANCER RESEARCH

Multidimensional communication of microRNAs and long non-coding RNAs in lung cancer

Tingting Guo[1] · Junyao Li[1] · Lin Zhang[1] · Wei Hou[1] · Rongrong Wang[1] · Jie Zhang[1] · Peng Gao[1]

Received: 28 June 2018 / Accepted: 6 October 2018 / Published online: 11 November 2018

Abstract

Purpose Non-coding RNAs (ncRNAs) have been a hot topic for many years in the field of cancer research, especially miRNAs and lncRNAs. Because they play critical roles in regulating various cellular processes and are more often involved in tumorigenesis than protein-coding genes. But the cross talk between miRNAs and lncRNAs in cancer has been scarcely studied. This article aims to provide a retrospective review of the latest research on the link between miRNAs and lncRNAs in lung cancer and discusses their potential role as diagnostic biomarkers and therapeutic targets for lung cancer in clinical practice.

Methods We reviewed literatures about ncRNAs and lung cancer from PUBMED databases in this article.

Results As shown in our review, miRNAs and lncRNAs could represent underlying targets for diagnosis, therapy, prognosis, and drug resistence of lung cancer. By acting as ceRNAs, lncRNAs can competitively inhibit the expression levels of miRNAs, and the lncRNA/miRNA axis can contribute to tumorigenesis, metastasis, and mutidrug resistance in lung cancer via various classic signaling pathways or related proteins.

Conclusion Based on present knowledge, ncRNAs may provide a novel perspective to understand the pathogenesis of lung cancer and could be candidates in screening of therapeutic targets for lung cancer.

Keywords microRNAs · Long non-coding RNAs · Lung cancer · Tumorigenesis · EMT

Introduction

Lung cancer is one of the most lethal malignant tumors with a 5-year survival rate after diagnosis as low as 18%, and most cases of lung cancer (about 80%) are non-small cell lung cancers (NSCLCs) (Devesa et al. 2005; Jemal et al. 2011; Siegel et al. 2018). Lung cancer has been the leading cause of cancer-related death in both men and women, and the occurrence rate remains at a high level. Cancer statistics (Siegel et al. 2018) shows that lung cancer most frequently occurs in the age group from 50 to 59 years. As many factors are involved in tumorigenesis and tumor progression in addition to hereditary factors, the pathogenetic mechanism of lung cancer is complicated and not fully understood (Basumallik and Agarwal 2018). Major risk factors for lung cancer are smoking, asbestos, radon, and other environmental factors. Current treatments for lung cancer, such as surgical exeresis, medical treatment, and radiotherapeutic interventions, provide little improvement in the survival rate of patients. The major reasons for this failure are the high molecular heterogeneity of lung cancer and that fact that

✉ Jie Zhang
doctorzhangj@sina.com

✉ Peng Gao
gaopeng1234@sina.com

Tingting Guo
guott8901@163.com

Junyao Li
lijunyao191@126.com

Lin Zhang
zhanglin9202@126.com

Wei Hou
641404919@qq.com

Rongrong Wang
905643072@qq.com

[1] Department of Respiratory Medicine, The Second Hospital of Jilin University, 218 Ziqiang Street, Nanguan District, Changchun 130041, Jilin, P.R. China

current diagnostic methods relying on low-dose computed tomography (CT) scanning (National Lung Screening Trial Research et al. 2011) and classic serum cancer markers are limited and unspecific; therefore, lung cancer is usually diagnosed at an advanced stage (Reck et al. 2013). Thus, there is an urgent need to identify new molecules that allow precise diagnosis of lung cancer and advance the development of anticancer drugs for targeted treatment in lung cancer. Recent studies have shown that the expression patterns of miRNAs and lncRNAs are greatly changed in a cancer background, indicating their potential as new biomarkers in lung cancer diagnosis. Many miRNAs and lncRNAs, such as miR-135b, miR-21, and lnc H19, have been tested in clinical treatments as targets to suppress the development of tumor (Alexius-Lindgren et al. 2014; Amit and Hochberg 2010; Yao et al. 2017), fueling optimism for lung cancer therapy targeting miRNAs or lncRNAs. In this context, it is important to understand the mechanism of both miRNAs and lncRNAs in lung cancer.

Non-coding RNAs (ncRNAs) were first discovered in the 1960s with the development of human transcriptome analysis (Papageorgiou et al. 2016), and subsequent research refuted the previous conclusion that most of the human genome encodes protein-coding genes by showing that non-coding RNAs can play important roles (International Human Genome Sequencing 2004). According to the number of nucleotides, ncRNAs were classified into three groups: small ncRNAs of 15–30 nts, which include microRNAs (miRNAs), piwi-interacting RNAs (piRNA Le Thomas et al. 2014), and transcription initiation RNAs; medium-size ncRNAs of 30–200 nts; and long ncRNAs (lncRNAs) with a length of over 200 nts. The effects of miRNAs on translational processes have been recognized for a long time (Inui et al. 2010; Kapralova et al. 2014; Kozomara and Griffiths-Jones 2011). More recent developments in high-resolution microarray and massively parallel sequencing technology showed that an increasing number of lncRNAs had evolutionarily conserved features (Guttman et al. 2009; Ponjavic et al. 2007). Moreover, many lncRNAs have been detected in serum, plasma, and other body fluids, thus providing potential novel biomarkers for cancer diagnosis and treatment, although the molecular regulatory mechanisms of lncRNAs in cancers remain to be elucidated (Ge et al. 2013; Iguchi et al. 2015; Jin et al. 2015; Li et al. 2013). We unexpectedly found communication between miRNAs and lncRNAs in the cancer condition. In this review, we summarize some miRNAs and lncRNAs that are important in lung cancer, discuss their mechanisms of action, and propose possible modes of communication between these miRNAs and lncRNAs.

MicroRNA in lung cancer

MicroRNAs are single-stranded evolutionarily conserved ncRNAs present in a ribonucleoprotein complex called the RNA-induced silencing complex (RISC) that targets the 3′ untranslated region (UTR) of mRNAs, resulting in blockage of translation or promotion of mRNA transcript degradation. The biogenesis of miRNAs is known to be a complex process (Fig. 1). The dysregulation of miRNAs is intricate and currently not fully understood, but probably depends on the alteration of cancer-related genomic regions or fragile sites, epigenetic changes, and numerous Pol II-related

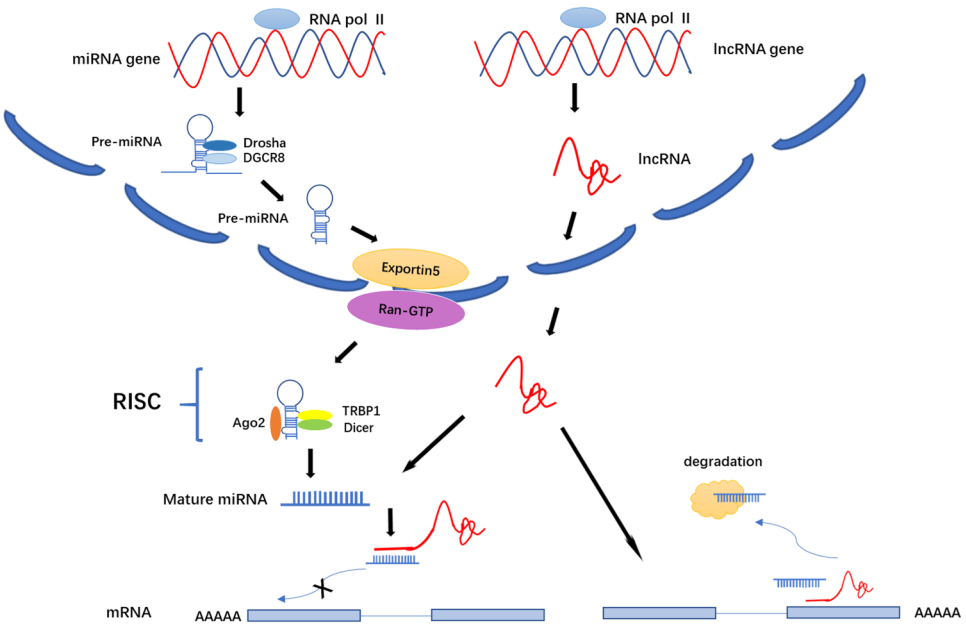

Fig. 1 Biogenesis of miRNAs and lncRNAs that act as sponges for miRNAs. Both miRNAs and lncRNAs are transcribed by RNA polymerase II. miRNAs are derived from primary miRNAs several hundred nucleotides in length, which are cleaved and processed to become 20 and 25 nt-long miRNA duplexes. The resultant miRNAs are incorporated into the RNA-induced silencing complex (RISC), which targets mRNA and affects translational activities. lncRNAs interact directly with miRNAs to inhibit binding of miRNA to the 3′ UTR of target mRNA or indirectly by binding to the 3′ UTR of the target mRNA, which promotes degradation of the miRNA

factors (Zhou et al. 2017). A large number of miRNAs such as miR-21 (Hatley et al. 2010; Medina et al. 2010) and miR-155 (Costinean et al. 2006; O'Connell et al. 2008) have been shown to play vital roles in pathological processes including cancer occurrence and development and the regulation of tumor cell proliferation, metastasis, invasion, and apoptosis via participation in most cancer-related signaling pathways or by targeting tumor oncogenes or tumor suppressors (Ambros 2003; Hwang and Mendell 2006).

Regarding research methods, quantitative real-time reverse transcription PCR (qRT-PCR) and the dual-luciferase reporter system are the most common methods for detecting the expression of miRNAs and analyzing the relationship between miRNAs and target mRNAs (McDougall et al. 1972; Sun et al. 2012). With the development of biochip technology, circulating miRNAs in serum, plasma, urine, and other human body fluids can be detected in bulk via high-throughput profiling techniques (Hu et al. 2010). Zhang et al. assessed the lung cancer miRNAs/RNAseq dataset from The Cancer Genome Atlas (TCGA) to obtain an miRNA–mRNA network. Their data showed that 116 miRNAs and 502 mRNAs were dysregulated in lung tumor tissues compared to adjacent non-tumor tissues, of which 70 miRNAs and 136 mRNAs were upregulated, while 46 miRNAs and 366 mRNAs were downregulated (Zhang et al. 2017e). It is likely that more aberrant miRNAs in lung cancer will be identified in future research.

Previous studies have confirmed the potential of miRNAs as sensitive and specific biomarkers in the diagnosis and prognosis of lung cancer; moreover, this application is not limited to only serum. Many miRNAs have been studied for early detection of lung cancer using serum including miR-23b, miR-221, miR-148b, miR-423-3p, let-7, miR-331-3p, miR-29a-3p, miR-148a-3p, miR-223-3p, and miR-140-5p (Chu et al. 2018; Jin et al. 2017a; Montani et al. 2015). A study showing that miR-223 was upregulated whereas miR-212 was downregulated in sputum samples of patients opened up a potential new noninvasive approach for the detection of lung cancer (Bagheri et al. 2017). Zhang's study showed that the area under the curve (AUC) values of miR-205-5p, miR-3917, miR-27a-5p, miR-30a-3p, miR-30a-5p, miR-30c-2-3p, and miR-30d-5p were 0.728, 0.661, 0.637, 0.758, 0.772, 0.734, and 0.776, respectively for the diagnosis of lung cancer (Zhang et al. 2017e). Table 1 lists the major microRNAs that are potential biomarkers for lung cancer. Furthermore, Su et al. put forward the concept that miRNA profiles in sputum are different from those in peripheral blood mononuclear cells (PBMC) in lung cancer based on repeated comparison, further complicating the role of miRNAs in different body fluids in lung tumorigenesis (Su

Table 1 Major microRNAs as potential biomarkers for lung cancer

MicroRNA	Expression	Detectable location	Biomarker category	Target gene
let-7	Downregulation	Tissue/plasma	Diagnostic/prognostic/chemoresistance	RAS, CDK6, cyclin-D, LIN28, MYC, HMGA2, HOXA9, TGFBR1, BCL-XL, MAP4K3
miR-135b	Upregulation	Tissue	Prognostic/chemoresistance	IL-1R1, EGFR, FZD1, MID1, MTCH2
miR-200	Upregulation/downregulation	Tissue/serum	Prognostic/chemoresistance	ZEB, E-cadherin, vimentin, FSCN1, Notch-1
miR-494	Upregulation	Tissue/serum	Prognostic/chemoresistance	IGF2BP1, BIM
miR-155	Upregulation	Tissue	Diagnostic/prognostic/chemoresistance	BACH1, PDCD4, hexokinase 2, APAf-1, SOCS1, SOCS6, and PTEN
miR-153	Downregulation	Tissue	Prognostic	ADAM19, AKT
miR-101	Downregulation	Tissue	Prognostic/chemoresistance	PTCH1, COX-2, Lin28B, EZH2, Wnt/β-catenin signaling pathway
miR-218	Downregulation	Tissue	Prognostic/chemoresistance	IL-6, STAT3, HMGB1, Slug/ZEB2, tumor protein D52, ADAM9
miR-34	Downregulation	Tissue/serum	Prognostic/chemoresistance	p53, PDL1, PDGFR-α/β
miR-21	Upregulation	Tissue/serum	Diagnostic/prognostic/chemoresistance	TLR4, ROS, FBP1, SOCS1, SOCS6, PTEN, COX-19, BTG2
miR-126	Downregulation	Tissue/serum	Diagnostic/prognostic/chemoresistance	SLC7A5, PTEN, PI3K, AKT, VEGFA
miR-22	Downregulation	Tissue/serum	Diagnostic/prognostic	Snail, ZEB, E-cadherin, vimentin
miR-24-3p	Upregulation	Tissue	Chemoresistance	SOX7, SOX18, ATG4A
miR-429	Upregulation	Tissue/plasma	Diagnostic/prognostic	DLC-1
miR-613	Upregulation	Plasma	Chemoresistance	CDK4
miR-451	Downregulation	Tissue	Prognostic/chemoresistance	RAB14, c-Myc, surviving, rad-51
miR-31	Upregulation	Tissue/serum	Diagnostic/prognostic	HuR, BAP1, ABCB9, KRAS, PI3K

et al. 2018). Exosome-associated miRNAs, a group of small RNAs that are transported and delivered by extracellular vesicles, have been an active topic of research in different solid cancers, such as breast cancer, melanoma, and lung cancer, and are proposed to function in tumor progression and metastasis, promotion of tumor cell growth, suppression of the immune system response, and induction of angiogenesis (Bortoluzzi et al. 2017; Kosaka et al. 2013; Sato-Kuwabara et al. 2015). Together, these results suggest that miRNAs may deliver some information or act as a kind of stimulant or suppressant of factors in cell-to-cell communication and thus promote establishment and maintenance of the tumor microenvironment. To date, miRNAs are known to be involved in lung inflammatory mechanisms, epithelial–mesenchymal transition, and some classic cancer signaling pathways, and studies are beginning to elucidate the roles of individual miRNAs in lung cancer (Calura et al. 2016; Nana-Sinkam and Geraci 2006). In addition, a single miRNA can target different mRNAs or one mRNA can be targeted by various miRNAs, resulting in an intricate network of cross talk between miRNAs and mRNAs in lung cancer.

Finally, mutations in miRNAs have been widely studied in lung cancer, showing that miRNAs play an active role in the genesis and development of lung cancer and can predict lung cancer occurrence and prognosis. Here, we review the characteristics of several common miRNAs in lung cancer.

Let-7

Let-7 RNA was first identified in *C. elegans* (Reinhart et al. 2000) and is a 21-nucleotide ncRNA that has been shown to be abnormally expressed in many cancers such as prostate, breast, ovarian, and lung cancer (Shin et al. 2016; Wagner et al. 2014; Wendler et al. 2011; Yan et al. 2014) and target various related genes or pathways (Wang et al. 2012). The expression of let-7 is downregulated in lung cancer and significantly associated with shorter survival (Shin et al. 2016; Xia et al. 2010). Sequenom mass spectrometry-based genotyping assay showed that an SNP of let-7, rs1143770C>T, was associated with better survival in early non-small cell lung cancer (Xia et al. 2010). In mechanism research, reduced expression of let-7 promoted side population (SP) cell differentiation, which can produce most cancer stem cells (CSCs) and participate in many types of human malignancies (Hua et al. 2012). KRAS alteration can disturb the expression of let-7, increasing the risk of various cancers (Kim et al. 2014; Kundu et al. 2012). In addition, a double negative feedback loop formed by LIN28B and let-7 has been identified; dysfunction of MUC1-C impacts the LIN28B → let-7 → HMGA2 axis and is involved in epithelial–mesenchymal transition (EMT) and self-renewal capacity of NSCLC cells (Alam et al. 2015). The demonstration that PCAF, a gene that mediates Lin28B acetylation, increased let-7a-1 and let-7g expression may shed light on the potential application of let-7 inhibitors in the clinical treatment of lung cancer patients (Qu et al. 2018).

miR-135b

miR-135b shows potential as a prognostic marker and molecular treatment target in lung cancer. miR-135b was markedly upregulated in invasive lung adenocarcinoma compared to adenocarcinoma in situ/minimally invasive adenocarcinoma (AIS/MIA), and its expression was higher in the EGFR mutated group than in the EGFR wild-type group (Le et al. 2017). Suppression of miR-135b by the natural compound morin reduced lung tumor cell viability, colony formation, and migration rate, and directly repressed the target gene CCNG2 (Yao et al. 2017), indicating that miRNAs are a promising therapeutic target. Lung adenocarcinomas with EGFR mutations and miR-135b overexpression are more likely to invade visceral pleura, opening a novel direction of study into the molecular mechanism of invasiveness (Le et al. 2017).

miR-21

Previous studies in lung cancer cell lines showed that locked nucleic acid (LNA)-based miR-21 (anti-miR-21) significantly inhibited tumor proliferation and promoted cell apoptosis in A549 cells through apoptotic signaling (Xu et al. 2014) or inhibition of NADPH oxidase (Yan et al. 2015). The in vivo effect of anti-miR-21 was examined in a xenograft tumor model, in which the tumor growth curve was recorded and immunohistochemistry of the xenograft tumor was performed. As expected, miR-21 inhibitor suppressed NSCLC growth in the xenograft model (Alexius-Lindgren et al. 2014). This finding may implicate miRNA-21 as a novel therapeutic target for lung cancer; however, large-scale clinical studies should be performed to support this hypothesis and the side effects are unknown. Through meta-analysis, Wu et al. evaluated the diagnostic value of miR-21 in 676 patients with lung cancer and 529 healthy controls from 11 research articles, obtaining sensitivity of 0.66 (95% confidence interval Alexius-Lindgren et al. 2014: 0.57–0.74), specificity of 0.82 (95% CI 0.74–0.88), and AUC of 0.81 (95% CI 0.77–0.84). These values indicate that the diagnostic efficiency of miR-21 alone is not ideal and either additional miRNAs should be used or miRNA-21 analysis should be combined with other diagnostic systems (Wu et al. 2014).

miR-200

The miR-200 family contains five members (mir-200a, mir-200b, mir-200c, mir-141, and mir-429), which are widely

known to be associated with the epithelial–mesenchymal transition (EMT) process and have an inhibitory or stimulatory role in many kinds of tumors (Si et al. 2017). Lin et al. analyzed the miRNA expression profiles of 418 lung adenocarcinoma (LUAD) cases obtained from the TCGA dataset, showing that a panel of four miRNAs (mir-600, mir-200a, mir-200b, and mir-548b) from lung tumor tissue were linked to pathologic N and overall stage (Lin et al. 2016). miR-200c, a member of the miR-200 family located on chromosome 12p13, was overexpressed in NSCLC tissues and significantly associated with lymph node metastasis, and the results of Cox regression multivariate analysis demonstrated that the combination of high miR-200c expression with TNM stage could be considered an independent prognostic factor (Si et al. 2017). Conversely, in another study the expression of miR-200c decreased during tumor progression, suggesting a tumor suppressor function (Ceppi et al. 2010). Moreover, a previous study reported that the mir-200ba/429 cluster could be expressed in a wavelike manner during carcinogenesis (Meng et al. 2015). Therefore, expression of the miR-200 family in lung cancer may have a polytropic trend and the corresponding outcome could vary accordingly.

miR-126

miRNA-126 (miR-126), also called miR-126-3p, is an endothelial miRNA (Ebrahimi et al. 2014) that is highly expressed in highly vascularized tissues where it plays a critical role in angiogenesis and maintenance of vascular integrity and is downregulated in NSCLC patients (Lin et al. 2012; Wang et al. 2008). A novel panel of four miRNAs (miR-182, miR-183, miR-210, and miR-126) was selected for detection of early-stage lung cancer in serum from 112 NSCLC patients and 104 controls by RT-PCR (Zhu et al. 2016). A combination of these four miRNAs with carcinoembryonic antigen (CEA) further increased the diagnostic value, with an AUC of 0.965. Decreased expressed miR-126 could distinguish NSCLC patients from healthy controls, current smokers, and pneumonia patients (Zhu et al. 2016). Interestingly, Grimolizzi et al. reported increased expression of exosomal miR-126 in NSCLC patients at both early and late stages of the disease and suggested a role in the formation of new blood vessels and participation in intercellular communication in the tumor microenvironment (Grimolizzi et al. 2017; Kosaka et al. 2016). miR-126-enriched exosomes were shown to be transported into A549 cells, where they regulated the downstream targets insulin receptor substrate-1 (IRS1) and vascular endothelial growth factor (VEGF), thus inhibiting cell growth and transformation (Grimolizzi et al. 2017). Exosomal miR-126 provides an efficacious personalized therapeutic modality and offers new insight into the mechanism of lung cancer development with respect to the tumor microenvironment.

LncRNA in lung cancer

Long non-coding RNAs (lncRNAs) are a class of non-coding RNAs longer than 200 nucleotides that play a crucial role in regulating various aspects of genome activity. lncRNA was originally considered transcriptional noise. In the early 1990s, lncRNA H19 and lncRNA Xist were studied in relation to epigenetic regulation (Brannan et al. 1990; Brockdorff et al. 1992; Brown et al. 1992). Similar to mRNAs, lncRNAs are transcribed by RNA polymerase II and some lncRNAs also have the structural features of a 5′-7-methylguanosine cap and 3′-poly(A) tail, even though they have no potential to encode proteins (Ernst and Morton 2013; Gibb et al. 2011; Guo et al. 2016). lncRNAs can be divided into five major types according to their genomic location relative to nearby protein-coding genes (Fig. 2).

Unlike small ncRNAs and many protein-encoding genes, lncRNA sequences show weak conservation of sequences that maintain functional domains and structures, accounting for the diversity and complexity of lncRNA functions (Chaumeil et al. 2011; Liu et al. 2014). lncRNAs regulate the expression of various genes by multiple mechanisms, including epigenetic change (Mercer and Mattick 2013), mRNA splicing (Tripathi et al. 2010), lncRNA-microRNA interaction (Steck et al. 2012), lncRNA–protein interaction (Watanabe and Yamamoto 1994), and lncRNA–mRNA interaction (Yuan et al. 2014). A growing amount of research has described many functions for lncRNAs in various cellular processes, such as gene imprinting (Kanduri 2016), differentiation and development (Fatica and Bozzoni 2014), and antiviral response (Fortes and Morris 2016). The importance of lncRNAs in human disease has been implicated by many studies, especially in cancer. lncRNAs play an important role in tumorigenesis and tumor-suppressive processes. Zhong et al. reported that the lncRNA PANDAR was upregulated in many types of cancer, including colorectal cancer, lung cancer, renal cell carcinoma, cholangiocarcinoma, osteosarcoma, and thyroid cancer. Moreover, overexpression of PANDAR was significantly associated with clinical factors such as tumor weight, TNM stage, and overall survival (Zou et al. 2018). The phenotype of diseases is also related to the abnormal structure of ncRNAs. Recently, researchers have found that N6-methyladenosine (m6A) modification had the effect on gene expression, and disrupting this regulation would lead to occurrence of diseases. Liu et al. believed that m6A altered the secondary structure of RNAs, making certain RNA-binding proteins easy to access the RNA sequence, and thus interfered with modification and eventually regulated gene expression. They observed that

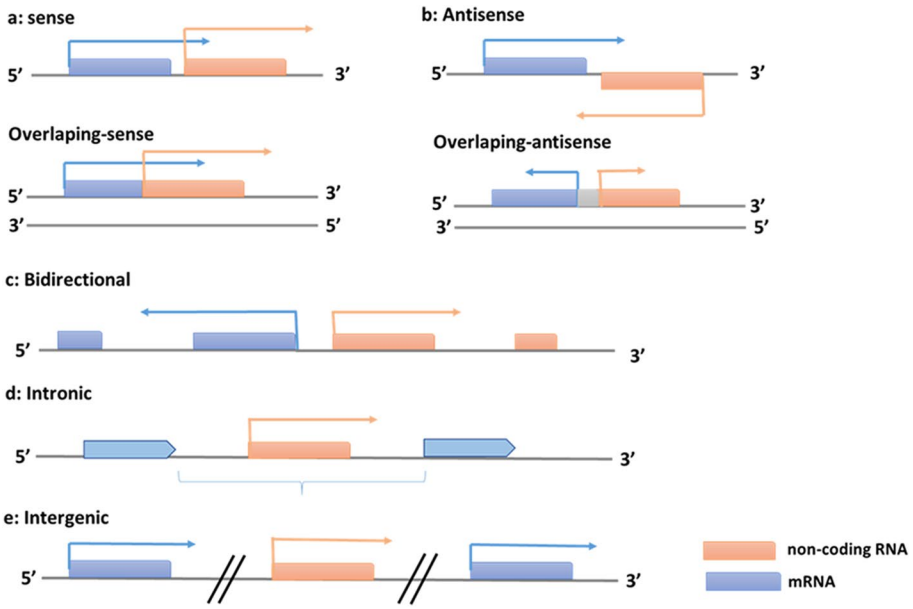

Fig. 2 Classification of ncRNAs based on their genomic location. **a** Sense lncRNAs and overlapping sense lncRNAs located in the same strand as exons of protein-coding genes. **b** Antisense lncRNAs and overlapping antisense lncRNAs are transcribed in the opposite strand from protein-coding genes. **c** Bidirectional lncRNAs are initiated in a reverse fashion from the promoter of a neighboring protein-coding gene. **d** Intronic lncRNAs are initiated inside an intron of a protein-coding gene in either direction and terminate without overlapping exons. **e** Intergenic lncRNAs (also termed large intervening non-coding RNAs or linRNAs) behave as genomic interval units between two protein-coding genes

methylation of the m6A site on transcriptional MALAT1 altered the structure of the stem loop by breaking the balance of base pairs and increasing the length of the loop containing a single chain of uracil nucleotide, which made the binding site easier to bind to the HNRNPC protein (Theler and Allain 2015). In addition, the proteins collected by m6A can be used as writers, readers, and erasers in ncRNAs modification. For example, YTHDC1, as an m6A reader protein, is a mediator of the X-chromosome silencing effect of lnc XIST (Patil et al. 2016). RBM15/15B, as an m6A writer protein, could directly methylate lnc XIST. The mutation of RBM15 was associated with the pathogenesis of borderline/malignant phyllodes tumors and played a key function on the development of various blood diseases, such as acute/chronic myeloid leukemia and Kaposi's sarcoma (Garcia-Dios et al. 2018; Patil et al. 2016). In glioblastoma tumorigenesis, lnc FOXM1-AS facilitated the function of ALKBH5 which was an eraser m6A protein and demethylated nascent FOXM1 transcripts. This m6A modulators indicated poor clinical outcome in GBM patients and different ALKBH5 expression levels in established and primary glioma cell lines represented different stages of malignancy (Zhang et al. 2017c). Therefore, how m6A participates in the modification and expression of ncRNAs may be a great progress in the studies of cancer occurrence and development. In transcriptomic profiling, researchers found that 114 lncRNAs were significantly differentially expressed between late-stage and early-stage lung squamous cell carcinoma (LSCC) and 8 lncRNAs were significantly associated with the overall survival of LSCC patients, suggesting great potential for screening using individual lncRNAs or panels of lncRNAs as biomarkers in the diagnosis and prognosis of lung cancer (Wang et al. 2018). Table 2 lists lncRNAs associated with the diagnosis and prognosis of NSCLC. In the recent era of precision oncology, ncRNA replacement therapy has been utilized as an innovative therapeutic strategy because of its many advantages, but more clinical trials are required to solve the technological challenges and address safety concerns (Tian et al. 2017). Moreover, in recent years, the dysregulation of lncRNAs has been highlighted as a novel mechanism of lung cancer resistance (Cheng et al. 2015; Yang et al. 2013). Table 3 lists the lncRNAs associated with drug resistance of NSCLC. For most lncRNAs, the exact mechanism of their function in lung cancer tumorigenesis remains a mystery.

The above findings indicate that lncRNAs can not only serve as biomarkers on lung cancer, but also be targets in lung cancer therapy. Below, we will describe some lncRNAs that are aberrantly expressed in lung cancer.

Lnc H19

H19 is located at chromosome 11p15.5 and its expression is elevated in numerous cancers, most likely through epigenetic

Table 2 LncRNAs associated with the diagnosis and prognosis of NSCLC

LncRNA	Expression pattern	Biomarker category	Key factors and pathway	Functions
PCAT6	Upregulated	Diagnostic/prognostic	c-Myc and p53	Plasma levels of PCAT6 significantly increased in NSCLC; negatively correlates with overall survival of lung cancer patients
H19	Upregulated	Prognostic		Contributes to the progression of NSCLC, expression levels can reflect invasive and metastatic status, associated with disease-free survival time
LINC00961	Downregulated	Prognostic	LSD1, β-catenin	Associated with advanced clinical stage, lymph node metastasis, and shorter survival time of NSCLC patients
HOTAIR	Upregulated	Diagnostic		Combination of HOTAIR and CEA might provide a more accurate diagnosis than HOTAIR or CEA alone (AUC = 0.841, 95% CI 0.783–0.898)
NEAT1	Upregulated	Diagnostic/prognostic	CTR1, Wnt signal pathway, mir-98-5p, MAPK6, miR-377-3p	Significantly increased in plasma samples of NSCLC patients; NSCLC patients with high NEAT1 expression show significantly shorter overall survival
HOTTIP	Upregulated	Prognostic	miR-574-5p, EZH1	Correlated with clinical stage and shorter survival time of SCLC patients
AFAP1-AS1	Upregulated	Diagnostic/prognostic	AFAP1 and KRT1	Promotes cell proliferation, independent predictor for disease-free survival in patients with lung adenocarcinoma
ROR	Upregulated	Prognostic		Higher lnc-ROR expression levels positively correlate with advanced TNM stage, positive distant metastasis, 5-year overall survival, and disease-free survival
SOX21-AS1	Upregulated	Prognostic	p57	Independent prognostic factor for overall survival of LUAD
MALAT-1	Upregulated	Diagnostic/prognostic	Bcl-2	Exosomal MALAT-1 highly expressed in NSCLC patients, associated with tumor stage and lymphatic metastasis
BCAR4	Upregulated	Prognostic	Vimentin, N-cadherin and E-cadherin	Associated with lymph node metastasis, clinical stage, poor 5-year overall survival rate of NSCLC patients
SFTA1P	Downregulated	Diagnostic/prognostic		New target for lung adenocarcinoma diagnosis; correlated with poor survival time of lung adenocarcinoma patients
CCAT1	Upregulated	Diagnostic	c-Myc, let-7c	Involved in cigarette smoke extract-induced malignant transformation of HBE cells
GAS5	Downregulated	Prognostic	Transcription factor E2F1, p53	Potential combined biomarker for screening NSCLC and patient monitoring after surgical treatment
XIST	Upregulated	Diagnostic/prognostic	E-cadherin, Bcl-2, miR-449a	Functions as a miRNA sponge of miR-449a, which is a negative regulator of Bcl-2. ROC curves between NSCLC patients and control group show AUC of 0.834 for XIST
ZXF1	Upregulated	Prognostic	BMP-5 and SCFR	Correlated with tumor differentiation, lymph node metastasis, and poor survival
LINC00152	Upregulated	Prognostic	IL24, EZH2	Correlated with advanced TNM stage, larger tumor size, and lymph node metastasis, as well as shorter survival time

Table 2 (continued)

LncRNA	Expression pattern	Biomarker category	Key factors and pathway	Functions
CASC2	Downregulated	Diagnostic/prognostic		Correlated with advanced TNM stage and tumor size. Multivariate analyses found that CASC2 expression served as an independent predictor for overall survival of NSCLC
GAS6-AS1	Downregulated	Diagnostic/prognostic		Correlated with lymph node metastasis and advanced tumor node metastasis stage; independent predictor for overall survival
HNF1A-AS1	Upregulated	Prognostic	DNMT1, cyclin D1, E-cadherin, N-cadherin, and β-catenin	Associated with TNM stage and lymph node metastasis, predicts unfavorable overall survival
ATB	Upregulated	Prognostic		Promotes cell viability, migration, and invasion; high expression of lncRNA-ATB associated with lower survival probability
LincRNA-p21	Downregulated	Prognostic		Affects outcome in patients with NSCLC adenocarcinoma through the regulation of angiogenesis; high lincRNA-p21 levels associated with poor cancer-specific survival in NSCLC patients
SBF2-AS1	Upregulated	Prognostic		Associated with NSCLC histological grade, lymph node metastasis, and overall survival times
TUBA4B	Downregulated	Prognostic		Regulates cell proliferation; correlated with advanced TNM stage and lymph node metastasis and serves as a predictor for overall survival of NSCLC
LUCAT1	Upregulated	Prognostic	p21 and p57	Associated with poor prognosis; affects cell proliferation
AGAP2-AS1	Upregulated	Prognostic	LATS2 and KLF2	Negatively correlated with poor prognostic outcomes
UCA1	Upregulated	Prognostic	miR-193a-3p, ERBB4	Higher expression of UCA1 led to a significantly poorer survival time
ANRIL	Upregulated	Diagnose/prognostic	KLF2 and P21	Associated with higher TNM stage and advanced lymph node metastasis; plasma ANRIL shows high diagnostic performance with ROC AUC of 0.798
BANCR	Downregulated	Prognostic	p38 MAPK and JNK	Correlated with tumor size and advanced TNM stage; independent predictor for overall survival
CARLo-5	Upregulated	Prognostic		Promotes proliferation, migration, and invasion in NSCLC cell lines; regulates EMT; patients with high CARLo-5 expression have significantly poorer prognosis
SPRY4-IT1	Upregulated	Diagnose/prognostic	EZH2	Promotes NSCLC cell proliferation and metastasis by affecting EMT; circulating SPRY4-IT1 significantly increased in plasma samples of NSCLC patients
Sox2ot	Upregulated	Prognostic	Cyclin B1 and Cdc2, EZH2	Predicts poor survival in lung cancer patients
MVIH	Upregulated	Prognostic	MMP2 and MMP9	Correlated with TNM stages, tumor size, and lymph node metastasis; serves as an independent risk factor to predict poor RFS; promotes tumor growth and metastasis

Table 2 (continued)

LncRNA	Expression pattern	Biomarker category	Key factors and pathway	Functions
MEG3	Downregulated	Prognostic	MDM2 and p53	Decreases NSCLC cell proliferation and induces apoptosis; patients with lower levels of MEG3 expression showed relatively poor prognosis

Table 3 LncRNAs associated with drug resistance of NSCLC

LncRNA	Expression pattern in drug-resistant cell	Key factors and pathway	Functions
MALAT1	Upregulated	miR-101 and SOX9	MALAT1, miR-101, and SOX9 form a feedback loop that enhances the chemoresistance of lung cancer cells to DDP
SNHG12	Upregulated	miR-181a, MAPK1, and MAP2K1	Multidrug resistance (MDR) in NSCLC
XIST	Upregulated	miR-17	Potential marker of poor response to cisplatin chemotherapy, promotes autophagy by regulation of ATG7
MEG3	Downregulated	miR-21-5p, SOX7, p53, WNT/β-catenin signaling pathway, p53, and Bcl-xl	Enhances DDP sensitivity of NSCLC cells
AK001796	Upregulated	CCNC and BIRC5 (apoptosis-associated factors); CDK1 and GTSE5 (cell cycle-associated factors)	Potential marker of poor response to cisplatin chemotherapy
CCAT1	Upregulated	miR-130a-3p, SOX4, ABCG2, let-7c, Bcl-xl	DDP resistance and docetaxel resistance of NSCLC cells
GAS5	Downregulated	miR-21, PTEN pathway, EGFR pathway, IGF-1R proteins	Regulation of chemosensitivity of NSCLC cell to DDP; resistance to gefitinib
TRPM2-AS	Upregulated	p53-p66shc pathway	A549/DDP cells show remarkably higher expression of lnc TRPM2-AS than paired A549 cells
KCNQ1OT1	Upregulated		Chemoresistance to paclitaxel
ROR	Upregulated	PI3K, Akt, mTOR, and bcl-2, miR-145, FSCN1	Involved in cisplatin resistance, regulates docetaxel-resistant LAD cells via EMT
AK001796	Upregulated		Regulates cellular cisplatin resistance and cell viability
CASC9	Upregulated		Involved in the sensitivity of PC9G cells to gefitinib
EWAST1	Downregulated		Regulates sensitivity of PC9G cells to gefitinib
BC087858	Upregulated	ZEB1 and Snail, PI3K/AKT and MEK/ERK pathways	Induces non-T790M mutation acquired resistance to EGFR-TKIs
NEAT1	Upregulated	hsa-mir-98-5p	Upregulates EGCG-induced CTR1 and enhances cisplatin sensitivity
HOTAIR	Upregulated	DNMT1 and DNMT3b, P21	Mediates chemoresistance of SCLC by regulating HOXA1 methylation
UCA1	Upregulated	AKT/mTOR pathway	May induce non-T790M acquired resistance to EGFR-TKIs by activating the AKT/mTOR pathway and EMT
AK126698	Upregulated	NKD2, Wnt/β-catenin signaling	Confers cisplatin resistance by targeting the Wnt pathway

changes (Ayesh et al. 2002; Kondo and Takahashi 1996). In lung cancer, hypomethylation of the H19 promoter region was frequently observed, which may explain its pivotal role in NSCLC environmental carcinogenesis including chronic exposure to tobacco, mineral dust, and other environmental carcinogens (Chen et al. 2013; Kondo et al. 1995). In addition, lncRNA H19 contributes to the progression of NSCLC and is associated with disease-free survival (DFS) time, and its expression levels can reflect the invasive and metastatic status (Zhang et al. 2016a). Mechanistically, apart from directly regulating cancer-associated pathways, H19 acts as a molecular sponge to suppress many miRNAs, such as miR-138 and miR-200a (Ayesh et al. 2002; Liang et al. 2015). Among lncRNAs, H19 has become a priority in cancer therapy. A vector expressing diphtheria toxin A-fragment (DTA) under the control of H19 and IGF2-P4 regulatory sequences

on a single construct for targeted bladder cancer therapy was confirmed in vivo and heterotopic and orthotopic bladder tumor models (Amit and Hochberg 2010). However, more appropriate animal models are needed to validate the efficacy of this vector before clinical application.

LNC MALAT1

MALAT1 is an 8.7-kb intergenic lncRNA located on chromosome 11q13 that is also known as nuclear-enriched abundant transcript 2 (NEAT2). MALAT1 has been utilized as a prognostic biomarker (Ji et al. 2003). The expression of lncRNA MALAT1 is upregulated in various kinds of cancer such as liver, uterus, lung, breast, and prostate cancer (Zhang et al. 2015). The expression of MALAT-1 was correlated with proliferation and metastasis of tumor cells, poorer overall survival (OS), and even development of brain metastasis in lung cancer patients (Ji et al. 2003). Zhang et al. demonstrated that classic lncRNA MALAT-1 was protected by exosomes, and the AUC for serum exosomal MALAT-1 receiver operator characteristic curve (ROC) reached 0.703 with a sensitivity of 0.601 and a specificity of 0.809 (Zhang et al. 2017b). This result gave hints on a novel relationship between lncRNA and the tumor microenvironment for exploring the therapeutic approaches to lung cancer. In addition, a feedback loop consisting of MALAT1, miR-101, and SOX9 was confirmed to enhance the chemo-resistance of lung cancer cells to DDP (Chen et al. 2017), indicating the multiple roles of MALAT1 in lung cancer.

TUG1

The expression of TUG1 is upregulated in hepatocellular carcinoma, esophageal squamous cell carcinoma, and osteosarcoma (Huang et al. 2015; Xu et al. 2015; Zhang et al. 2013), and downregulated in lung cancer (Zhang et al. 2014a), indicating that TUG1 might play a dual role as an oncogene/tumor suppressor in human tumors. However, Liu et al. recently reported that TUG1 was significantly upregulated in lung adenocarcinoma (LAD) cells and serum samples with an AUC of 0.756 compared with 0.619 for cyfra21-1 by receiver operator characteristic (ROC) analysis (Liu et al. 2017). The expression pattern and function of TUG1 vary according to different histopathological types in lung cancer, and further research is needed to confirm this association. Functionally, as an anti-tumor gene, TUG1 might epigenetically modulate the expression of HOXB7 by binding to PRC2, thus activating the AKT and MAPK pathways (Zhang et al. 2014a). In contrast, knockdown of TUG1 suppressed LAD cell viability and promoted cell apoptosis by targeting BAX to induce apoptosis (Liu et al. 2017). Studies on the expression and mechanism of many lncRNAs, including TUG1, are still immature, and most research on lncRNAs has been restricted to their expression level.

GAS5

GAS5, located at 1q25, was first isolated from NIH3T3 cells (Coccia et al. 1992) and later shown to perform a suppressive role in cancer cell proliferation, invasion, and/or metastasis. By quantitative real-time PCR (QRT-PCR), the expression of GAS5 in tissue and serum was decreased in NSCLC and sharply increased in postoperative groups compared to patients without surgery (Tan et al. 2017). In addition to its diagnostic value, GAS5 showed a possible role in chemoresistance of lung cancer. Zhang et al. reported that downregulation of GAS5 was associated with cisplatin resistance in NSCLC, through a mechanism involving autography (Zhang et al. 2016b). Moreover, GAS5 was upregulated in lung cancer cells treated with 5-aza-2-deoxy-cytidine (Shi et al. 2015). Overexpression of GAS5 inhibited high glucose (HG)-induced proliferation by promoting the ubiquitin-mediated degradation of TRIB3 protein (Ding et al. 2018). Epigenetic regulation plays a role in abnormal expression of lncRNAs, in addition to be involved in regulation of their downstream genes.

MEG3

MEG3 located on chromosome 14q32.3 acts as an anti-tumor factor and was found to participate in various cellular processes (Roth and Diederichs 2016). Like GAS5, the expression of MEG3 could be silenced by hypermethylation (Zhang et al. 2010). Kruer et al. showed that MEG3 expression was regulated by the pRb pathway and mainly associated with its downstream DNA methyltransferase 1 (DNMT1) (Kruer et al. 2016). Treatment with palbociclib targeting the active pRb pathway also led to a change in methylation of the MEG3 promoter, supporting the notion that methylation may be involved in suppression of MEG3 (Kruer et al. 2016) and implying that expression of lncRNA was primarily impacted by epigenetic regulation. Furthermore, Kaplan–Meier survival analysis of data from the Gene Expression Omnibus (GEO) database containing 1144 NSCLC patients suggested that low MEG3 expression could be a poor prognostic factor for shorter overall survival (OS) in NSCLC (Zhang et al. 2017f).

The interaction between lncRNA and miRNA in lung cancer

Previous studies have uncovered connections between miRNAs/lncRNAs and tumor development and progression in lung cancer. With recent progress in molecular analytical

and sequencing technologies, the total miRNome/lncRNome can be quantified in a rapid and reliable manner, allowing investigators to identify specific expression profiles linked to the development of lung cancer. A competing endogenous network established based on information from the miRanda database and TargetScan contained 5 miRNAs, 41 circRNAs, 82 lncRNAs, and 211 genes, providing a novel insight into the complex molecular mechanisms of the miRNA-mediated gene regulatory network in lung cancer (Jin et al. 2017b). However, because of limited lncRNA expression profiles, it was difficult to determine the expression trends of lncRNAs in relation to the pathology of lung cancer. In addition, clinical experiments are needed to validate most of these risk factors. Nonetheless, the network completely and systematically showed the relationship between mRNAs, miRNAs, and lncRNAs and may serve as the basis for future experimental research in the area of lung cancer research.

lncRNAs act as endogenous sponges for miRNAs

A large group of lncRNAs, called competitive endogenous RNAs (ceRNAs), can compete with mRNAs for binding to microRNAs (Li et al. 2017a). The function of lncRNAs as ceRNAs is just like the molecular interactions between miRNAs and miRNA response elements (MREs), which are located in 3′ UTRs, coding sequences (CDS), and 5′ UTRs and inhibit the activity and expression of RNA molecules at the post-transcriptional level (Su et al. 2013; Xia et al. 2014), leading to transcription suppression or miRNAs degradation as shown in Fig. 1. The ceRNA networks play an important role in the occurrence and development of cancer, although the status of the field of ceRNAs is currently unclear because studies are still in their infancy. Many studies have proved that lncRNAs can function as ceRNAs to regulate microRNAs. For example, the lncRNA NEAT1 promoted E2F3 expression in part through competitive binding with miRNA-377-3p in lung cancer cells (Zhang et al. 2017a). Another study has demonstrated that NEAT1 can act as a competing endogenous lncRNA to regulate STAT3 by sponging up miR-485 in hepatocellular carcinoma (HCC) (Zhang et al. 2017d). NEAT1 can downregulate miR-129 by competitively binding to miR-129, thereby leading to the derepression of CTBP2, a target of miR-129, to promote esophageal squamous cell carcinoma (ESCC) cell progression (Li et al. 2017c). These findings showed that lncRNAs could act as sponges for multiple kinds of miRNA to regulate target gene expression in various cancers. There are multiple software programs that can be used to predict ceRNA target genes and various molecular biology methods such as luciferase reporter systems and co-immunoprecipitation assays have been used to validate computer predictions, providing an effective approach to elucidate the molecular mechanisms of certain ceRNA networks (Shuwen et al. 2018). The functions of lncRNAs as ceRNAs may provide a new direction to study the mechanism of lung cancer. Figure 3 shows the relationship between lncRNAs and miRNAs involved in ceRNA regulation in lung cancer.

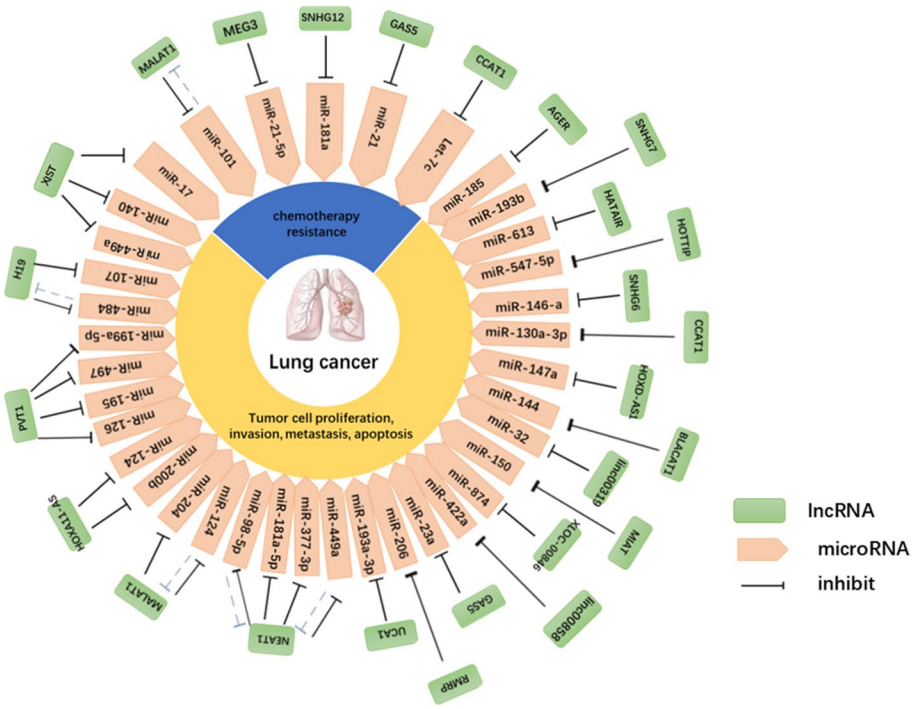

Fig. 3 Complex network between lncRNAs and miRNAs involved in ceRNA regulation in lung cancer. Regulation of the lncRNA/miRNA pathway in NSCLC can be classified into two main functional groups: tumor proliferation, invasion, metastasis, and apoptosis or chemotherapy resistance

miRNA–lncRNA pathways have a common end point of EMT

Epithelial–mesenchymal transition (EMT) is a widely existent biologic process in lung cancer that can polarize epithelial cells and change them to a mesenchymal cell phenotype, thus enhancing migratory capacity, promoting invasiveness, and inhibiting apoptosis (Kalluri and Neilson 2003). EMT is an important change in the occurrence and development of tumor and is involved in many signaling pathways. Terashima et al. found that expression of MEG3 was immediately and transiently induced by TGF-β, suggesting its potential role in the induction of EMT (Terashima et al. 2017). Members of the miR-200 family have been shown to inhibit EMT, cell migration, and invasion by targeting mRNA for ZEB1 and ZEB2, two repressors of E-cadherin expression (Park et al. 2008). In Terashima's study, TGF-β upregulated the expression of ZEB1 and ZEB2 and decreased the expression of two representative miRNAs, miR-200a and miR-200c. MEG3 knockdown itself slightly but significantly reduced the expression of ZEB1 and ZEB2 and increased the expression of miR-200a and miR-200c (Terashima et al. 2017). Similarly, the H19/miR-484 and MALAT1/miR-204 axes also played an active role in the process of EMT in lung cancer (Li et al. 2016; Zhang et al. 2018) (Fig. 4). In addition, hypoxia is another inducer of EMT and the H19/miR-675 axis could orchestrate EMT/MET phenotypes via miR-200 in the condition of hypoxia, promoting tumor cell invasion and metastasis through upregulation of HIF-α and downregulation of p53 (Matouk et al. 2015). However, to date the H19/miR-675 axis in lung cancer has not been covered.

lncRNAs/miRNAs co-regulate tumor-associated classic pathways

At present, tumor-associated classic pathways are the most important factors in the complex network and regulatory system of tumor formation and represent a breakthrough in conquering cancer. Since the expression of various lncRNAs is upregulated or downregulated in lung cancer tissues via multiple classic signaling pathways, such as Wnt/β-catenin signaling pathway (Sun et al. 2017), MAPK (Wang et al. 2017), or JNK (Zhang et al. 2018), which are also regulated by miRNAs, we can presume that lncRNAs/miRNAs co-regulate some of the classic tumor-related signal pathways. For example, STAT3 has been reported as a pivotal regulator of lung cancer malignancy (Li et al. 2015). In breast cancer stem cells, it has been demonstrated that MiR-7 suppressed EMT and metastasis through downregulation of the STAT3 pathway, which was inhibited indirectly by lncRNA HOTAIR (Zhang et al. 2014b). At the same time, Li's study showed that MALAT1 can modulate STAT3 expression by acting as a miR-124 sponge in NSCLC, but there was no detailed description of downstream genes of the STAT3 pathway (Li et al. 2017b). The p53 gene is one of the most highly cancer-correlated genes identified to date and is known to be an important tumor suppressor gene and a negative regulatory factor for cell cycle regulation, DNA damage repair, cell differentiation, apoptosis, senescence, and many other processes that play important biological roles. In bladder cancer, H19 negatively regulated miR-675, reversed cell cycle G1 arrest, and promoted tumor cell apoptosis via the p53 pathway (Liu et al. 2016). The H19/miR-140/iASPP axis was also shown to regulate glioma cell proliferation and invasion (Zhao et al. 2016). In lung cancer, XIST modulated tumor growth and metastasis via miR-140-dependent regulation of the p53 pathway (Tang et al. 2017). In terms of the chemo-sensitivity of NSCLC, miR-21 could impact GAS5's regulation of NSCLC sensitivity to DDP through

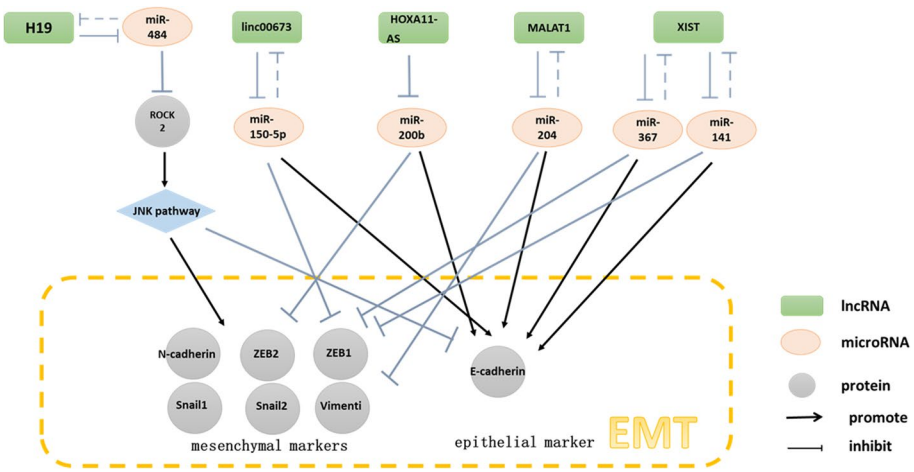

Fig. 4 Regulatory network of several lncRNAs that function as sponges for miRNAs associated with epithelial–mesenchymal transition in the pathogenesis of lung cancer

the PTEN pathway. At the same time, a high miR-21 expression and a low PTEN expression were found to be correlated with advanced TNM stages and larger tumor size (Cao et al. 2017). Besides, knockdown LINC00152 suppressed the progression of NSCLC tumor via EGFR/PI3K/AKT pathway, and H19 played an important role in the migration and invasion of NSCLC which was associated with the expression of EGFR, Wnt/β-catenin pathway, and ERK pathway (Wang et al. 2016). The JNK pathway, cAMP pathway, and MAPK/Slug pathway can be also regulated by the lncRNA/miRNA axis in lung cancer (Chen et al. 2016; Wang et al. 2017; Zhang et al. 2018). Although lncRNAs/miRNAs are known to regulate tumor-associated pathways, current researches are not comprehensive; for example, there are many pathways that are not yet confirmed in lung cancer, such as Ras or Notch signaling pathways, and more downstream genes associated with these pathways need to be explored in lung cancer. Therefore, much work is needed to clarify the communication between lncRNAs/miRNAs in lung cancer.

In the process of gene expression, ncRNAs can participate in different processes, and the abnormal expression of ncRNAs can make the protein-coding gene maladjusted, leading to diseases. In lung cancer, miR-484 suppressed H19 expression by directly binding to its 3′UTR, so knockdown miR-484 overexpressed H19 and its downstream molecule ROCK2 (Zhang et al. 2018). But in MDA-MB-231 cells, HOTAIR regulated the expression of miR-7 by inhibiting the HoxD10 expression which directly bound to the promoter of miR-7 and increased its expression (Zhang et al. 2014b). So, we can conclude that there are both direct and indirect communications between ncRNAs affecting their expression and function. In lung cancer, miR-21 could directly bind to GAS5 3′UTR. Interestingly, according to researchers' prediction and results, GAS5 and PTEN shared a similar binding site of miR-21, which suggested that GAS5 competed with PTEN for miR-21 binding (Cao et al. 2017). This is consistent with our findings that lncRNAs can act as ceRNAs competitively inhibiting miRNAs' expression. For the relationship between ncRNAs and their combined proteins, we discuss it from two aspects according to the characteristics of ncRNAs. When LncRNAs inhibited the translation of target mRNAs in cytoplasm, lincRNA-p21's level increased proportionately after silencing the RNA-binding protein HuR, which recruited let-7/RISC and accelerated lincRNA-p21 degradation (Yoon et al. 2012). Other studies have shown that translational regulatory lncRNA (treRNA) in cytoplasm could combine with RNA-binding proteins (hnRNP-K, FXR1, and FXR2), PUF60 and SF3B3, forming a treRNA–RNP complex and binding to translation initiation factor eIF4G1, leading to downregulation of the expression of the epithelial marker E-cadherin (Gumireddy et al. 2013). In nucleus, ncRNAs contact with heterogeneous nuclear ribonucleoproteins (hnRNPs) to regulate gene transcription. HnRNP-A/B and hnRNP-A2/B1 were identified as specific binding partners for lincRNA-Cox2 in both the nuclear and cytosolic fractions to repress the transcription of immune genes (Carpenter et al. 2013). Similarly, lincRNA-p21 could directly bind with hnRNP-K to compose a repressor complex that acts in the p53 pathway (Huarte et al. 2010). All these results revealed that ncRNAs could bind associated proteins impacting transcription and translation of target mRNAs through different ways in the cytoplasm and nucleus, making the regulatory network of ncRNAs more complicated.

It is becoming increasingly clear that lncRNAs and miRNAs are major actors in lung cancer. By acting as ceRNAs, lncRNAs can competitively inhibit the expression level of miRNAs, and the lncRNA/miRNA axis can contribute to tumorigenesis, metastasis, and multidrug resistance in lung cancer via various classic signaling pathways, of which the major process is probably EMT. In other cancers, scholars got similar results. For example, in epithelial ovarian cancer (EOC), Meng et al. detected four microRNAs (miR-7, miR-25, miR-93, and miR-429) that discriminated EOC patients from healthy women with a sensitivity of 93% and a specificity of 92% compared with CA125 in serum (Meng et al. 2015). Meanwhile, many lncRNAs such as HOTAIR, HOTTIP, and NEAT1 presented their function of contributing to tumor pathogenesis and progression in esophageal squamous cell carcinoma (ESCC) (Ge et al. 2013; Li et al. 2017c). In colorectal cancer, lncRNA H19 functioned as a ceRNA for miR-138 and miR-200a, antagonized their functions, and led to the de-repression of their endogenous targets vimentin, ZEB1, and ZEB2, regulating EMT (Liang et al. 2015). LncRNA HOTAIR indirectly downregulate miR-7 that inhibited SETDB1 and reversed the EMT via STAT3 pathway in breast cancer stem cells (Zhang et al. 2014b). HOTAIR also directly decreased WIF-1 expression by promoting its histone H3K27 methylation in the promoter region and then activated the Wnt/b-catenin signaling pathway in ESCC (Ge et al. 2013). So these results gave us a hint that we could infer the possible role of ncRNAs in lung cancer based on the known regulatory pathways of ncRNAs in other cancers. Despite ncRNAs' multiple regulation in lung cancer, there are still many questions to be answered. Methods for detecting the expression profiles of lncRNAs and miRNAs secreted in exosomes/body fluids and their potential use as diagnostic or prognostic tools for lung cancer patients must be elucidated. Ultimately, the development of targeted therapy involving lncRNAs/miRNAs will advance precision medicine in lung cancer.

At present, we focus on finding more ncRNAs and their biological functions in lung cancer, including their own communication and the regulation between them and DNA or proteins. In addition, the changes in the structure of ncRNAs, such as m6A and variable shearing, regulating gene expression and cell function are emerging topics of tumor

research. In clinical application, searching for ncRNAs that may become diagnostic markers and therapeutic targets is also the ultimate goal of our tumor research. However, some ncRNAs have high tissue specificity, but only a few molecular functions have been identified, and sometimes the expression levels of ncRNAs are none or little in cell lines, which is not sufficient for reliable quantification. Another question is that most of ncRNAs play a variety of roles in different subcellular domains, increasing the complexity of ncRNAs' research. In consequence, there is still a long way in ncRNAs' research, and to make clear the regulatory network of ncRNAs will be a major breakthrough in tumor treatment.

Conclusion

Numerous studies have confirmed that the aberrant expression of miRNAs and lncRNAs is significantly correlated to lung cancer diagnosis, prognosis, and therapeutic outcomes. The complexity and flexibility of the structures and functions of miRNAs and lncRNAs provide multiple possibilities regarding the mechanism of miRNAs/lncRNAs in the regulation of lung cancer. Furthermore, understanding the cross talk between mRNAs, miRNAs, and lncRNAs will yield promising functions of ncRNAs and possible communicative interaction in carcinogenesis, but requires a deeper understanding of their function and mechanism of action. Furthermore, for applications in clinical care, more animal experiments and clinical trials are needed. Based on present knowledge, we have summarized miRNAs and lncRNAs involved in lung cancer, described several miRNAs and lncRNAs with special or exploitable characters, and discussed the connection between miRNAs and lncRNAs and the unique functions of lncRNAs in competitive binding of microRNAs and regulation of their target genes. miRNAs and lncRNAs represent underlying targets for diagnosis, therapy, prognosis, and drug resistance of lung cancer and will help us learn more about the mechanism of tumor occurrence and progression. Our work may provide a novel perspective to understand the pathogenesis of lung cancer and lay the foundation to uncover new therapeutic targets for lung cancer.

Acknowledgements All data generated or analyzed during this study are included in this published article.

Author contributions JZ and PG contributed to the conception of the study. JL, LZ, WH, and RW contributed significantly to the analysis and manuscript preparation; TG performed the data analyses and wrote the manuscript. All authors read and approved the final manuscript.

Funding This work is partly supported by the National Natural Science Foundation of China (Grant no. 81672297).

Compliance with ethical standards

Conflict of interest The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval This article does not contain any studies with animals or human participants performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

Alam M, Ahmad R, Rajabi H, Kufe D (2015) MUC1-C induces the LIN28B → LET-7 → HMGA2 axis to regulate self-renewal in NSCLC. Mol Cancer Res 13:449–460. https://doi.org/10.1158/1541-7786.MCR-14-0363

Alexius-Lindgren M, Andersson E, Lindstedt I, Engstrom W (2014) The RECK gene and biological malignancy—its significance in angiogenesis and inhibition of matrix metalloproteinases. Anticancer Res 34:3867–3873

Ambros V (2003) MicroRNA pathways in flies and worms: growth, death, fat, stress and timing. Cell 113:673–676

Amit D, Hochberg A (2010) Development of targeted therapy for bladder cancer mediated by a double promoter plasmid expressing diphtheria toxin under the control of H19 and IGF2-P4 regulatory sequences. J Transl Med 8:134. https://doi.org/10.1186/1479-5876-8-134

Ayesh S et al (2002) Possible physiological role of H19. RNA Mol Carcinog 35:63–74. https://doi.org/10.1002/mc.10075

Bagheri A et al (2017) Altered miR-223 expression in sputum for diagnosis of non-small cell lung cancer. Avicenna J Med Biotechnol 9:189–195

Basumallik N, Agarwal M (2018) Cancer, lung, small cell (oat cell). StatPearls, Treasure Island

Bortoluzzi S, Lovisa F, Gaffo E, Mussolin L (2017) Small RNAs in circulating exosomes of cancer patients: a minireview. High Throughput. https://doi.org/10.3390/ht6040013

Brannan CI, Dees EC, Ingram RS, Tilghman SM (1990) The product of the H19 gene may function as an RNA. Mol Cell Biol 10:28–36

Brockdorff N et al (1992) The product of the mouse Xist gene is a 15 kb inactive X-specific transcript containing no conserved ORF and located in the nucleus. Cell 71:515–526

Brown CJ, Hendrich BD, Rupert JL, Lafreniere RG, Xing Y, Lawrence J, Willard HF (1992) The human XIST gene: analysis of a 17 kb inactive X-specific RNA that contains conserved repeats and is highly localized within the nucleus. Cell 71:527–542

Calura E et al (2016) Disentangling the microRNA regulatory milieu in multiple myeloma: integrative genomics analysis outlines mixed miRNA-TF circuits and pathway-derived networks modulated in t (4; 14) patients. Oncotarget 7:2367–2378. https://doi.org/10.18632/oncotarget.6151

Cao L, Chen J, Ou B, Liu C, Zou Y, Chen Q (2017) GAS5 knockdown reduces the chemo-sensitivity of non-small cell lung cancer (NSCLC) cell to cisplatin (DDP) through regulating miR-21/PTEN axis. Biomed Pharmacother 93:570–579. https://doi.org/10.1016/j.biopha.2017.06.089

Carpenter S et al (2013) A long noncoding RNA mediates both activation and repression of immune response genes. Science 341:789–792. https://doi.org/10.1126/science.1240925

Ceppi P, Mudduluru G, Kumarswamy R, Rapa I, Scagliotti GV, Papotti M, Allgayer H (2010) Loss of miR-200c expression induces an

aggressive, invasive, and chemoresistant phenotype in non-small cell lung cancer. Mol Cancer Res 8:1207–1216. https://doi.org/10.1158/1541-7786.MCR-10-0052

Chaumeil J, Waters PD, Koina E, Gilbert C, Robinson TJ, Graves JA (2011) Evolution from XIST-independent to XIST-controlled X-chromosome inactivation: epigenetic modifications in distantly related mammals. PLoS One 6:e19040. https://doi.org/10.1371/journal.pone.0019040

Chen B et al (2013) Mdig de-represses H19 large intergenic non-coding RNA (lincRNA) by down-regulating H3K9me3 and heterochromatin. Oncotarget 4:1427–1437. https://doi.org/10.18632/oncotarget.1155

Chen Z et al (2016) cAMP/CREB-regulated LINC00473 marks LKB1-inactivated lung cancer and mediates tumor growth. J Clin Investig 126:2267–2279. https://doi.org/10.1172/JCI85250

Chen W et al (2017) MALAT1-miR-101-SOX9 feedback loop modulates the chemo-resistance of lung cancer cell to DDP via Wnt signaling pathway. Oncotarget 8:94317–94329. https://doi.org/10.18632/oncotarget.21693

Cheng N et al (2015) Long non-coding RNA UCA1 induces non-T790M acquired resistance to EGFR-TKIs by activating the AKT/mTOR pathway in EGFR-mutant non-small cell lung cancer. Oncotarget 6:23582–23593. https://doi.org/10.18632/oncotarget.4361

Chu GCW, Lazare K, Sullivan F (2018) Serum and blood based biomarkers for lung cancer screening: a systematic review. BMC Cancer 18:181. https://doi.org/10.1186/s12885-018-4024-3

Coccia EM, Cicala C, Charlesworth A, Ciccarelli C, Rossi GB, Philipson L, Sorrentino V (1992) Regulation and expression of a growth arrest-specific gene (gas5) during growth, differentiation, and development. Mol Cell Biol 12:3514–3521

Costinean S, Zanesi N, Pekarsky Y, Tili E, Volinia S, Heerema N, Croce CM (2006) Pre-B cell proliferation and lymphoblastic leukemia/high-grade lymphoma in E(mu)-miR155 transgenic mice. Proc Natl Acad Sci USA 103:7024–7029. https://doi.org/10.1073/pnas.0602266103

Devesa SS, Bray F, Vizcaino AP, Parkin DM (2005) International lung cancer trends by histologic type: male: female differences diminishing and adenocarcinoma rates rising. Int J Cancer 117:294–299. https://doi.org/10.1002/ijc.21183

Ding CZ et al (2018) High glucose contributes to the proliferation and migration of non-small cell lung cancer cells via GAS5-TRIB3 axis. Biosci Rep. https://doi.org/10.1042/BSR20171014

Ebrahimi F, Gopalan V, Smith RA, Lam AK (2014) miR-126 in human cancers: clinical roles and current perspectives. Exp Mol Pathol 96:98–107. https://doi.org/10.1016/j.yexmp.2013.12.004

Ernst C, Morton CC (2013) Identification and function of long non-coding RNA. Front Cell Neurosci 7:168. https://doi.org/10.3389/fncel.2013.00168

Fatica A, Bozzoni I (2014) Long non-coding RNAs: new players in cell differentiation and development. Nat Rev Genet 15:7–21. https://doi.org/10.1038/nrg3606

Fortes P, Morris KV (2016) Long noncoding RNAs in viral infections. Virus Res 212:1–11. https://doi.org/10.1016/j.virusres.2015.10.002

Garcia-Dios DA et al (2018) MED12, TERT promoter and RBM15 mutations in primary and recurrent phyllodes tumours. Br J Cancer 118:277–284. https://doi.org/10.1038/bjc.2017.450

Ge XS et al (2013) HOTAIR, a prognostic factor in esophageal squamous cell carcinoma, inhibits WIF-1 expression and activates Wnt pathway. Cancer Sci 104:1675–1682. https://doi.org/10.1111/cas.12296

Gibb EA et al (2011) Human cancer long non-coding RNA transcriptomes. PLoS One 6:e25915. https://doi.org/10.1371/journal.pone.0025915

Grimolizzi F et al (2017) Exosomal miR-126 as a circulating biomarker in non-small-cell lung cancer regulating cancer progression. Sci Rep 7:15277. https://doi.org/10.1038/s41598-017-15475-6

Gumireddy K et al (2013) Identification of a long non-coding RNA-associated RNP complex regulating metastasis at the translational step. EMBO J 32:2672–2684. https://doi.org/10.1038/emboj.2013.188

Guo X, Gao L, Wang Y, Chiu DK, Wang T, Deng Y (2016) Advances in long noncoding RNAs: identification, structure prediction and function annotation. Brief Funct Genom 15:38–46. https://doi.org/10.1093/bfgp/elv022

Guttman M et al (2009) Chromatin signature reveals over a thousand highly conserved large non-coding RNAs in mammals. Nature 458:223–227. https://doi.org/10.1038/nature07672

Hatley ME, Patrick DM, Garcia MR, Richardson JA, Bassel-Duby R, van Rooij E, Olson EN (2010) Modulation of K-Ras-dependent lung tumorigenesis by MicroRNA-21. Cancer Cell 18:282–293. https://doi.org/10.1016/j.ccr.2010.08.013

Hu Z et al (2010) Serum microRNA signatures identified in a genome-wide serum microRNA expression profiling predict survival of non-small-cell lung cancer. J Clin Oncol 28:1721–1726. https://doi.org/10.1200/JCO.2009.24.9342

Hua S, Xiaotao X, Renhua G, Yongmei Y, Lianke L, Wen G, Yongqian S (2012) Reduced miR-31 and let-7 maintain the balance between differentiation and quiescence in lung cancer stem-like side population cells. Biomed Pharmacother 66:89–97. https://doi.org/10.1016/j.biopha.2011.09.013

Huang MD, Chen WM, Qi FZ, Sun M, Xu TP, Ma P, Shu YQ (2015) Long non-coding RNA TUG1 is up-regulated in hepatocellular carcinoma and promotes cell growth and apoptosis by epigenetically silencing of KLF2. Mol Cancer 14:165. https://doi.org/10.1186/s12943-015-0431-0

Huarte M et al (2010) A large intergenic noncoding RNA induced by p53 mediates global gene repression in the p53 response. Cell 142:409–419. https://doi.org/10.1016/j.cell.2010.06.040

Hwang HW, Mendell JT (2006) MicroRNAs in cell proliferation, cell death, and tumorigenesis. Br J Cancer 94:776–780. https://doi.org/10.1038/sj.bjc.6603023

Iguchi T et al (2015) A long noncoding RNA, lncRNA-ATB, is involved in the progression and prognosis of colorectal cancer. Anticancer Res 35:1385–1388

International Human Genome Sequencing C (2004) Finishing the euchromatic sequence of the human genome. Nature 431:931–945. https://doi.org/10.1038/nature03001

Inui M, Martello G, Piccolo S (2010) MicroRNA control of signal transduction. Nat Rev Mol Cell Biol 11:252–263. https://doi.org/10.1038/nrm2868

Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D (2011) Global cancer statistics. CA Cancer J Clin 61:69–90. https://doi.org/10.3322/caac.20107

Ji P et al (2003) MALAT-1, a novel noncoding RNA, and thymosin beta4 predict metastasis and survival in early-stage non-small cell lung cancer. Oncogene 22:8031–8041. https://doi.org/10.1038/sj.onc.1206928

Jin K et al (2015) Noncoding RNAs as potential biomarkers to predict the outcome in pancreatic cancer. Drug Des Dev Ther 9:1247–1255. https://doi.org/10.2147/DDDT.S77597

Jin X et al (2017a) Evaluation of tumor-derived exosomal miRNA as potential diagnostic biomarkers for early-stage non-small cell lung cancer using next-generation sequencing. Clin Cancer Res 23:5311–5319. https://doi.org/10.1158/1078-0432.CCR-17-0577

Jin X, Guan Y, Sheng H, Liu Y (2017b) Crosstalk in competing endogenous RNA network reveals the complex molecular mechanism underlying lung cancer. Oncotarget 8:91270–91280. https://doi.org/10.18632/oncotarget.20441

Kalluri R, Neilson EG (2003) Epithelial–mesenchymal transition and its implications for fibrosis. J Clin Investig 112:1776–1784. https://doi.org/10.1172/JCI20530

Kanduri C (2016) Long noncoding RNAs: lessons from genomic imprinting. Biochim Biophys Acta 1859:102–111. https://doi.org/10.1016/j.bbagrm.2015.05.006

Kapralova KH, Franzdottir SR, Jonsson H, Snorrason SS, Jonsson ZO (2014) Patterns of miRNA expression in Arctic charr development. PLoS One 9:e106084. https://doi.org/10.1371/journal.pone.0106084

Kim M et al (2014) Extensive sequence variation in the 3′ untranslated region of the KRAS gene in lung and ovarian cancer cases. Cell Cycle 13:1030–1040. https://doi.org/10.4161/cc.27941

Kondo M, Takahashi T (1996) Altered genomic imprinting in the IGF2 and H19 genes in human lung cancer. Nihon Rinsho Jpn J Clin Med 54:492–496

Kondo M, Suzuki H, Ueda R, Osada H, Takagi K, Takahashi T, Takahashi T (1995) Frequent loss of imprinting of the H19 gene is often associated with its overexpression in human lung cancers. Oncogene 10:1193–1198

Kosaka N, Iguchi H, Hagiwara K, Yoshioka Y, Takeshita F, Ochiya T (2013) Neutral sphingomyelinase 2 (nSMase2)-dependent exosomal transfer of angiogenic microRNAs regulate cancer cell metastasis. J Biol Chem 288:10849–10859. https://doi.org/10.1074/jbc.M112.446831

Kosaka N, Yoshioka Y, Fujita Y, Ochiya T (2016) Versatile roles of extracellular vesicles in cancer. J Clin Investig 126:1163–1172. https://doi.org/10.1172/JCI81130

Kozomara A, Griffiths-Jones S (2011) miRBase: integrating microRNA annotation and deep-sequencing data. Nucleic Acids Res 39:D152–D157. https://doi.org/10.1093/nar/gkq1027

Kruer TL, Dougherty SM, Reynolds L, Long E, de Silva T, Lockwood WW, Clem BF (2016) Expression of the lncRNA maternally expressed gene 3 (MEG3) contributes to the control of lung cancer cell proliferation by the Rb pathway. PLoS One 11:e0166363. https://doi.org/10.1371/journal.pone.0166363

Kundu ST, Nallur S, Paranjape T, Boeke M, Weidhaas JB, Slack FJ (2012) KRAS alleles: the LCS6 3′UTR variant and KRAS coding sequence mutations in the NCI-60 panel. Cell Cycle 11:361–366. https://doi.org/10.4161/cc.11.2.18794

Le Thomas A, Toth KF, Aravin AA (2014) To be or not to be a piRNA: genomic origin and processing of piRNAs. Genome Biol 15:204. https://doi.org/10.1186/gb4154

Le H et al (2017) Peripheral lung adenocarcinomas harboring epithelial growth factor receptor mutations with microRNA-135b overexpression are more likely to invade visceral pleura. Oncol Lett 14:7931–7940. https://doi.org/10.3892/ol.2017.7195

Li X, Wu Z, Mei Q, Li X, Guo M, Fu X, Han W (2013) Long noncoding RNA HOTAIR, a driver of malignancy, predicts negative prognosis and exhibits oncogenic activity in oesophageal squamous cell carcinoma. Br J Cancer 109:2266–2278. https://doi.org/10.1038/bjc.2013.548

Li X et al (2015) The tumor suppressor miR-124 inhibits cell proliferation by targeting STAT3 and functions as a prognostic marker for postoperative NSCLC patients. Int J Oncol 46:798–808. https://doi.org/10.3892/ijo.2014.2786

Li J et al (2016) LncRNA MALAT1 exerts oncogenic functions in lung adenocarcinoma by targeting miR-204. Am J Cancer Res 6:1099–1107

Li LJ, Zhao W, Tao SS, Leng RX, Fan YG, Pan HF, Ye DQ (2017a) Competitive endogenous RNA network: potential implication for systemic lupus erythematosus. Expert Opin Ther Targets 21:639–648. https://doi.org/10.1080/14728222.2017.1319938

Li S, Mei Z, Hu HB (2017b) The lncRNA MALAT1 contributes to non-small cell lung cancer development via modulating miR-124/STAT3 axis. J Cell Physiol. https://doi.org/10.1002/jcp.26325

Li Y, Chen D, Gao X, Li X, Shi G (2017c) LncRNA NEAT1 regulates cell viability and invasion in esophageal squamous cell carcinoma through the miR-129/CTBP2 axis. Dis Markers. https://doi.org/10.1155/2017/5314649

Liang WC et al (2015) The lncRNA H19 promotes epithelial to mesenchymal transition by functioning as miRNA sponges in colorectal cancer. Oncotarget 6:22513–22525. https://doi.org/10.18632/oncotarget.4154

Lin Q et al (2012) A cluster of specified microRNAs in peripheral blood as biomarkers for metastatic non-small-cell lung cancer by stem-loop RT-PCR. J Cancer Res Clin Oncol 138:85–93. https://doi.org/10.1007/s00432-011-1068-z

Lin K et al (2016) MicroRNA expression profiles predict progression and clinical outcome in lung adenocarcinoma. OncoTargets Ther 9:5679–5692. https://doi.org/10.2147/OTT.S111241

Liu HQ, Li Y, Irwin DM, Zhang YP, Wu DD (2014) Integrative analysis of young genes, positively selected genes and lncRNAs in the development of *Drosophila melanogaster*. BMC Evol Biol 14:241. https://doi.org/10.1186/s12862-014-0241-9

Liu C, Chen Z, Fang J, Xu A, Zhang W, Wang Z (2016) H19-derived miR-675 contributes to bladder cancer cell proliferation by regulating p53 activation. Tumour Biol 37:263–270. https://doi.org/10.1007/s13277-015-3779-2

Liu H et al (2017) Long noncoding RNA TUG1 is a diagnostic factor in lung adenocarcinoma and suppresses apoptosis via epigenetic silencing of BAX. Oncotarget 8:101899–101910. https://doi.org/10.18632/oncotarget.22058

Matouk IJ, Halle D, Gilon M, Hochberg A (2015) The non-coding RNAs of the H19-IGF2 imprinted loci: a focus on biological roles and therapeutic potential in lung cancer. J Transl Med 13:113. https://doi.org/10.1186/s12967-015-0467-3

McDougall JK, Dunn AR, Jones KW (1972) In situ hybridization of adenovirus RNA and DNA. Nature 236:346–348

Medina PP, Nolde M, Slack FJ (2010) OncomiR addiction in an in vivo model of microRNA-21-induced pre-B-cell lymphoma. Nature 467:86–90. https://doi.org/10.1038/nature09284

Meng X et al (2015) Diagnostic and prognostic potential of serum miR-7, miR-16, miR-25, miR-93, miR-182, miR-376a and miR-429 in ovarian cancer patients. Br J Cancer 113:1358–1366. https://doi.org/10.1038/bjc.2015.340

Mercer TR, Mattick JS (2013) Structure and function of long noncoding RNAs in epigenetic regulation. Nat Struct Mol Biol 20:300–307. https://doi.org/10.1038/nsmb.2480

Montani F et al (2015) miR-Test: a blood test for lung cancer early detection. J Natl Cancer Inst 107:djv063. https://doi.org/10.1093/jnci/djv063

Nana-Sinkam SP, Geraci MW (2006) MicroRNA in lung cancer. J Thorac Oncol 1:929–931

National Lung Screening Trial Research T et al (2011) Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 365:395–409 https://doi.org/10.1056/NEJMoa1102873

O'Connell RM et al (2008) Sustained expression of microRNA-155 in hematopoietic stem cells causes a myeloproliferative disorder. J Exp Med 205:585–594. https://doi.org/10.1084/jem.20072108

Papageorgiou N, Tslamandris S, Giolis A, Tousoulis D (2016) MicroRNAs in cardiovascular disease. Perspect Real Cardiol Rev 24:110–118. https://doi.org/10.1097/CRD.0000000000000078

Park SM, Gaur AB, Lengyel E, Peter ME (2008) The miR-200 family determines the epithelial phenotype of cancer cells by targeting the E-cadherin repressors ZEB1 and ZEB2. Genes Dev 22:894–907. https://doi.org/10.1101/gad.1640608

Patil DP, Chen CK, Pickering BF, Chow A, Jackson C, Guttman M, Jaffrey SR (2016) m^{6}A RNA methylation promotes XIST-mediated transcriptional repression. Nature 537:369–373. https://doi.org/10.1038/nature19342

Ponjavic J, Ponting CP, Lunter G (2007) Functionality or transcriptional noise? Evidence for selection within long noncoding RNAs. Genome Res 17:556–565. https://doi.org/10.1101/gr.6036807

Qu TT et al (2018) PCAF-mediated acetylation of Lin28B increases let-7 biogenesis in lung adenocarcinoma H1299 cells. BMC Cancer 18:27. https://doi.org/10.1186/s12885-017-3959-0

Reck M, Heigener DF, Mok T, Soria JC, Rabe KF (2013) Management of non-small-cell lung cancer: recent developments. Lancet 382:709–719. https://doi.org/10.1016/S0140-6736(13)61502-0

Reinhart BJ et al (2000) The 21-nucleotide let-7 RNA regulates developmental timing in *Caenorhabditis elegans*. Nature 403:901–906. https://doi.org/10.1038/35002607

Roth A, Diederichs S (2016) Long noncoding RNAs in lung cancer. Curr Top Microbiol Immunol 394:57–110. https://doi.org/10.1007/82_2015_444

Sato-Kuwabara Y, Melo SA, Soares FA, Calin GA (2015) The fusion of two worlds: non-coding RNAs and extracellular vesicles-diagnostic and therapeutic implications. Int J Oncol 46:17–27. https://doi.org/10.3892/ijo.2014.2712 **(Review)**

Shi X, Sun M, Liu H, Yao Y, Kong R, Chen F, Song Y (2015) A critical role for the long non-coding RNA GAS5 in proliferation and apoptosis in non-small-cell lung cancer. Mol Carcinog 54(Suppl 1):E1–E12 https://doi.org/10.1002/mc.22120

Shin KM et al (2016) The pri-let-7a-2 rs1143770C>T is associated with prognosis of surgically resected non-small cell lung cancer. Gene 577:148–152. https://doi.org/10.1016/j.gene.2015.11.036

Shuwen H, Qing Z, Yan Z, Xi Y (2018) Competitive endogenous RNA in colorectal cancer: a systematic review. Gene 645:157–162. https://doi.org/10.1016/j.gene.2017.12.036

Si L, Tian H, Yue W, Li L, Li S, Gao C, Qi L (2017) Potential use of microRNA-200c as a prognostic marker in non-small cell lung cancer. Oncol Lett 14:4325–4330. https://doi.org/10.3892/ol.2017.6667

Siegel RL, Miller KD, Jemal A (2018) Cancer statistics, 2018. CA Cancer J Clin 68:7–30. https://doi.org/10.3322/caac.21442

Steck E, Boeuf S, Gabler J, Werth N, Schnatzer P, Diederichs S, Richter W (2012) Regulation of H19 and its encoded microRNA-675 in osteoarthritis and under anabolic and catabolic in vitro conditions. J Mol Med (Berl) 90:1185–1195. https://doi.org/10.1007/s00109-012-0895-y

Su X, Xing J, Wang Z, Chen L, Cui M, Jiang B (2013) microRNAs and ceRNAs: RNA networks in pathogenesis of cancer. Chin J Cancer Res 25:235–239. https://doi.org/10.3978/j.issn.1000-9604.2013.03.08

Su J et al (2018) Integrating circulating immunological and sputum biomarkers for the early detection of lung cancer. Biomark Cancer 10:1179299. https://doi.org/10.1177/1179299X18759297

Sun Y, Gregory KJ, Chen NG, Golovlev V (2012) Rapid and direct microRNA quantification by an enzymatic luminescence assay. Anal Biochem 429:11–17. https://doi.org/10.1016/j.ab.2012.06.021

Sun SJ, Lin Q, Ma JX, Shi WW, Yang B, Li F (2017) Long non-coding RNA NEAT1 acts as oncogene in NSCLC by regulating the Wnt signaling pathway. Eur Rev Med Pharmacol Sci 21:504–510

Tan Q et al (2017) Identification of circulating long non-coding RNA GAS5 as a potential biomarker for non-small cell lung cancer diagnosisnon-small cell lung cancer, long non-coding RNA, plasma, GAS5, biomarker. Int J Oncol 50:1729–1738. https://doi.org/10.3892/ijo.2017.3925

Tang Y, He R, An J, Deng P, Huang L, Yang W (2017) lncRNA XIST interacts with miR-140 to modulate lung cancer growth by targeting iASPP. Oncol Rep 38:941–948. https://doi.org/10.3892/or.2017.5751

Terashima M, Tange S, Ishimura A, Suzuki T (2017) MEG3 long noncoding RNA contributes to the epigenetic regulation of epithelial-mesenchymal transition in lung cancer cell lines. J Biol Chem 292:82–99. https://doi.org/10.1074/jbc.M116.750950

Theler D, Allain FH (2015) Molecular biology: RNA modification does a regulatory two-step. Nature 518:492–493. https://doi.org/10.1038/518492a

Tian H, Zhou C, Yang J, Li J, Gong Z (2017) Long and short noncoding RNAs in lung cancer precision medicine: opportunities challenges. Tumour Biol. https://doi.org/10.1177/1010428317697578

Tripathi V et al (2010) The nuclear-retained noncoding RNA MALAT1 regulates alternative splicing by modulating SR splicing factor phosphorylation. Mol Cell 39:925–938. https://doi.org/10.1016/j.molcel.2010.08.011

Wagner S, Ngezahayo A, Murua Escobar H, Nolte I (2014) Role of miRNA let-7 and its major targets in prostate cancer. Biomed Res Int. https://doi.org/10.1155/2014/376326

Wang S et al (2008) The endothelial-specific microRNA miR-126 governs vascular integrity and angiogenesis. Dev Cell 15:261–271. https://doi.org/10.1016/j.devcel.2008.07.002

Wang X, Cao L, Wang Y, Wang X, Liu N, You Y (2012) Regulation of let-7 and its target oncogenes. Oncol Lett 3:955–960. https://doi.org/10.3892/ol.2012.609 **(Review)**

Wang L et al (2016) Targeting H19 by lentivirus-mediated RNA interference increases A549 cell migration and invasion. Exp Lung Res 42:346–353. https://doi.org/10.1080/01902148.2016.1223229

Wang P, Chen D, Ma H, Li Y (2017) LncRNA SNHG12 contributes to multidrug resistance through activating the MAPK/Slug pathway by sponging miR-181a in non-small cell lung cancer. Oncotarget 8:84086–84101. https://doi.org/10.18632/oncotarget.20475

Wang Y, Yang F, Zhuang Y (2018) Identification of a progression-associated long non-coding RNA signature for predicting the prognosis of lung squamous cell carcinoma. Exp Ther Med 15:1185–1192. https://doi.org/10.3892/etm.2017.5571

Watanabe Y, Yamamoto M (1994) *S. pombe* mei2+ encodes an RNA-binding protein essential for premeiotic DNA synthesis and meiosis I, which cooperates with a novel RNA species meiRNA. Cell 78:487–498

Wendler A, Keller D, Albrecht C, Peluso JJ, Wehling M (2011) Involvement of let-7/miR-98 microRNAs in the regulation of progesterone receptor membrane component 1 expression in ovarian cancer cells. Oncol Rep 25:273–279

Wu R et al (2014) Diagnostic value of microRNA-21 in the diagnosis of lung cancer: evidence from a meta-analysis involving 11 studies. Tumour Biol 35:8829–8836. https://doi.org/10.1007/s13277-014-2106-7

Xia XM, Jin WY, Shi RZ, Zhang YF, Chen J (2010) Clinical significance and the correlation of expression between Let-7 and K-ras in non-small cell lung cancer. Oncol Lett 1:1045–1047. https://doi.org/10.3892/ol.2010.164

Xia T, Liao Q, Jiang X, Shao Y, Xiao B, Xi Y, Guo J (2014) Long noncoding RNA associated-competing endogenous RNAs in gastric cancer. Sci Rep 4:6088. https://doi.org/10.1038/srep06088

Xu L, Huang Y, Chen D, He J, Zhu W, Zhang Y, Liu X (2014) Down-regulation of miR-21 increases cisplatin sensitivity of non-small-cell lung cancer. Cancer Genet 207:214–220. https://doi.org/10.1016/j.cancergen.2014.04.003

Xu Y et al (2015) Upregulation of the long noncoding RNA TUG1 promotes proliferation and migration of esophageal squamous cell carcinoma. Tumour Biol 36:1643–1651. https://doi.org/10.1007/s13277-014-2763-6

Yan Y, Zhang F, Fan Q, Li X, Zhou K (2014) Breast cancer-specific TRAIL expression mediated by miRNA response elements of let-7 and miR-122. Neoplasma 61:672–679. https://doi.org/10.4149/neo_2014_082

Yan S et al (2015) Inhibition of NADPH oxidase protects against metastasis of human lung cancer by decreasing microRNA-21.

Anticancer Drugs 26:388–398. https://doi.org/10.1097/CAD.0000000000000198

Yang Y, Li H, Hou S, Hu B, Liu J, Wang J (2013) The noncoding RNA expression profile and the effect of lncRNA AK126698 on cisplatin resistance in non-small-cell lung cancer cell. PLoS One 8:e65309. https://doi.org/10.1371/journal.pone.0065309

Yao D, Cui H, Zhou S, Guo L (2017) Morin inhibited lung cancer cells viability, growth, and migration by suppressing miR-135b and inducing its target CCNG2. Tumour Biol. https://doi.org/10.1177/1010428317712443

Yoon JH et al (2012) LincRNA-p21 suppresses target mRNA translation. Mol Cell 47:648–655. https://doi.org/10.1016/j.molcel.2012.06.027

Yuan JH et al (2014) A long noncoding RNA activated by TGF-beta promotes the invasion-metastasis cascade in hepatocellular carcinoma. Cancer Cell 25:666–681. https://doi.org/10.1016/j.ccr.2014.03.010

Zhang X et al (2010) Maternally expressed gene 3, an imprinted noncoding RNA gene, is associated with meningioma pathogenesis and progression. Cancer Res 70:2350–2358. https://doi.org/10.1158/0008-5472.CAN-09-3885

Zhang Q, Geng PL, Yin P, Wang XL, Jia JP, Yao J (2013) Down-regulation of long non-coding RNA TUG1 inhibits osteosarcoma cell proliferation and promotes apoptosis. Asian Pac J Cancer Prev 14:2311–2315

Zhang EB et al (2014a) P53-regulated long non-coding RNA TUG1 affects cell proliferation in human non-small cell lung cancer, partly through epigenetically regulating HOXB7 expression. Cell Death Dis 5:e1243. https://doi.org/10.1038/cddis.2014.201

Zhang H et al (2014b) MiR-7, inhibited indirectly by lincRNA HOTAIR, directly inhibits SETDB1 and reverses the EMT of breast cancer stem cells by downregulating the STAT3 pathway. Stem Cells 32:2858–2868. https://doi.org/10.1002/stem.1795

Zhang J, Zhang B, Wang T, Wang H (2015) LncRNA MALAT1 overexpression is an unfavorable prognostic factor in human cancer: evidence from a meta-analysis. Int J Clin Exp Med 8:5499–5505

Zhang E, Li W, Yin D, De W, Zhu L, Sun S, Han L (2016a) c-Myc-regulated long non-coding RNA H19 indicates a poor prognosis and affects cell proliferation in non-small-cell lung cancer. Tumour Biol 37:4007–4015. https://doi.org/10.1007/s13277-015-4185-5

Zhang N, Yang GQ, Shao XM, Wei L (2016b) GAS5 modulated autophagy is a mechanism modulating cisplatin sensitivity in NSCLC cells. Eur Rev Med Pharmacol Sci 20:2271–2277

Zhang J, Li Y, Dong M, Wu D (2017a) Long non-coding RNA NEAT1 regulates E2F3 expression by competitively binding to miR-377 in non-small cell lung cancer. Oncol Lett 14:4983–4988. https://doi.org/10.3892/ol.2017.6769

Zhang R et al (2017b) Serum long non coding RNA MALAT-1 protected by exosomes is up-regulated and promotes cell proliferation and migration in non-small cell lung cancer. Biochem Biophys Res Commun 490:406–414. https://doi.org/10.1016/j.bbrc.2017.06.055

Zhang S et al (2017c) m^6A demethylase ALKBH5 maintains tumorigenicity of glioblastoma stem-like cells by sustaining FOXM1 expression and cell proliferation program. Cancer Cell 31:591–606 e596. https://doi.org/10.1016/j.ccell.2017.02.013

Zhang XN, Wang CC, Zhou J (2017d) The long noncoding RNA NEAT1 contributes to hepatocellular carcinoma development by sponging miR-485 and enhancing the expression of the STAT3. J Cell Physiol. https://doi.org/10.1002/jcp.26371

Zhang Y et al (2017e) Differential expression profiles of microRNAs as potential biomarkers for the early diagnosis of lung cancer. Oncol Rep 37:3543–3553. https://doi.org/10.3892/or.2017.5612

Zhang Z et al (2017f) Down-regulation of long non-coding RNA MEG3 indicates an unfavorable prognosis in non-small cell lung cancer: evidence from the GEO database. Gene 630:49–58. https://doi.org/10.1016/j.gene.2017.08.001

Zhang Q, Li X, Li X, Li X, Chen Z (2018) LncRNA H19 promotes epithelial-mesenchymal transition (EMT) by targeting miR-484 in human lung cancer cells. J Cell Biochem 119:4447–4457. https://doi.org/10.1002/jcb.26537

Zhao H et al (2016) The lncRNA H19 interacts with miR-140 to modulate glioma growth by targeting iASPP. Arch Biochem Biophys 610:1–7. https://doi.org/10.1016/j.abb.2016.09.014

Zhou Q et al (2017) MicroRNAs: a novel potential biomarker for diagnosis and therapy in patients with non-small cell lung cancer. Cell Prolif. https://doi.org/10.1111/cpr.12394

Zhu W et al (2016) Diagnostic value of serum miR-182, miR-183, miR-210, and miR-126 levels in patients with early-stage non-small cell lung cancer. PLoS One 11:e0153046. https://doi.org/10.1371/journal.pone.0153046

Zou Y et al (2018) Long non-coding PANDAR as a novel biomarker in human cancer: a systematic review. Cell Prolif. https://doi.org/10.1111/cpr.12422