Review Article

Long non-coding RNAs in non-small cell lung cancer: functions and distinctions from other malignancies

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Abstract: Lung cancer leads to the most cancer-related death in the world. It was shown from the increasing evidences that long non-coding RNAs (lncRNAs) are emerging as molecules for diagnosis, prognosis and even therapy of lung cancer and other malignancies. The biological functions or involved signaling pathways of lncRNAs are always found to be inconsistent among different types of malignancies. However, no available literature has systemically summarized differences in the functions and underlying molecular mechanisms of lncRNAs between lung cancer and other cancers. In this review, the biological functions and molecular mechanisms of lncRNAs in lung cancer were introduced. Furthermore, their functional differences between lung cancer and other malignancies were discussed. Finally, their potential clinical applications in future lung cancer therapy were focused on.

Keywords: Lung cancer; long non-coding RNAs (lncRNAs); biomarkers; targeted therapy

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Introduction

In the long history of medical science, the cancer has always been troubling us as the most insurmountable disease. Lung cancer is one of the most lethal and prevalent cancers in the world, which is reported to cause 26% of all cancer-related deaths (1). However, there are still some limitations in current therapy approaches (surgery, chemotherapy and radiotherapy), such as high recurrence rates and serious side effects. Furthermore, effective clinical approaches are still lacked for early-stage diagnosis. In order to improve therapeutic effect and decrease high lethality of lung malignancy, it is urgently needed to discover new biomarkers and therapeutic targets.

According to the classical theory of the central dogma, the RNA molecule is considered as a template for protein synthesis. Although all of the genome is expected to be transcribed into RNA, only 5–10% of the genome can be transcribed. During the transcription, the protein coding RNAs only account for lower than 10% due to evolutionary conservation (2). Distinct from protein-coding RNAs, the large group of RNAs is lack of protein-coding function, and therefore, they are designated as non-coding RNAs (ncRNA). Accumulated evidences have demonstrated that ncRNAs have effects on the regulation of transcription or pre-mRNA processing, even some ncRNAs can interact with proteins (3). During the last decade, the emerging of ncRNAs has opened a new field for both basic and clinical oncologists.

NcRNAs are classified into small non-coding RNAs and long non-coding RNAs (lncRNAs). In general, the former is featured with a length of shorter than 200 nt, which consists of microRNA (miRNA), small nuclear RNA (snRNA), small interfering RNA (siRNA), Piwi interacting RNA (piRNA), transfer RNA (tRNA) and ribosomal RNA (rRNA). Whereas, lncRNAs comprise a group of transcripts and they are longer than 200 nucleotides. According to

their genomic locations, lncRNAs can be subdivided into intergenic and intragenic lncRNAs (lincRNA). LincRNAs are further classified as exonic, intronic and overlapping lncRNAs (4). Interestingly, several lncRNAs have been reported to be actually the precursor of other small RNAs (5). Unlike extensively studied miRNAs in Cancer Res, the association between lncRNAs and malignancies is relatively less characterized.

Thousands of lncRNAs are screened in human's transcriptome, and however, only dozens of them have been well studied, such as X-inactive specific transcript (XIST), HOX transcript antisense RNA (HOTAIR), nuclear enriched abundant transcript 1 (NEAT1), and metastasis associated lung adenocarcinoma transcript 1 (MALAT1). LncRNAs have shared characteristics with mRNA. For examples, they are both transcribed by RNA polymerase II and usually followed by splicing. Their mature molecules have both capped 5' termini and polyadenylated 3' termini. The only difference between lncRNAs and mRNAs is that lncRNAs are lack of a protein-coding potential (6).

It was shown from many studies that lncRNAs can modulate specific gene expression, and they are thus involved in various biological processes of cancer cells. Moreover, the increasing evidences show that the lncRNA play a key role in cancer initiation, progression, and metastasis (7). On the basis of previous studies, we found that one lncRNA always relates to different signaling pathways or biological functions in different types of malignancies. Therefore, researching the functional differences of lncRNAs in multiple malignancies including lung cancer is an important work for further understanding the etiology and pathology of cancer.

In this review, dozens of known lung-cancer-associated lncRNAs were summarized, and their roles in lung cancer biology were described. Firstly, the biological functions and molecular mechanism of these lncRNAs in lung cancer were presented. Furthermore, their functional differences between lung cancer and other malignancies were discussed. Finally, their potential clinical applications in future lung cancer therapy were focused on.

Action mechanisms of lncRNAs in cancers

So far, the known molecular mechanisms by which lncRNAs affect cell functions involve interfering of transcription, initiation of chromatin remodeling, and silencing of gene clusters (8,9). In this part, the molecular mechanisms of lncRNA functions (*Figure 1*) were described.

Roughly, lncRNAs exert their functions on affecting transcription via pre-transcriptional, transcriptional and post-transcriptional levels. At pre-transcription level, the regulation of lncRNAs on genome involves histone modification, DNA methylation, X-chromosome inactivation, gene imprinting, and chromosome dosage compensation. For instance, XIST, a well-studied lncRNA, regulates dosage compensation in female mammals. After localized to the X chromosome, XIST can recruit multiple factors indirectly to execute X chromosome inactivation (XCI) (10-13). At transcription level, lncRNAs can affect transcription of neighboring genes and genes on different chromosomes (11,14). According to the study, NEAT1 binds to the promoter region of oncogenic genes to increases their transcription (15). LncRNA may also cooperate with transcription factors to regulate the transcription of target genes. For example, p53-inducible lincRNA-p21 directly binds to hnRNP-K, and in turn, mediates gene repression during cellular response to DNA damage (13). At post-transcriptional level, lncRNAs always act as a competing endogenous RNAs (ceRNA) by competitively binding miRNAs (small non-coding RNAs located in cytoplasm, which always target 3' UTR of mRNAs to degrade them or prevent their translation), and consequently, they indirectly protect their predestinated mRNAs from being silencing or degraded (16,17). In addition, lncRNAs also affect translation by influencing the alternative splicing of pre-mRNAs (5). Notably, some lncRNAs can improve the stability of mRNA via their complementary sequences with target molecules, without involving miRNAs (18).

Furthermore, depending on their subcellular localizations, lncRNAs can be classified into nuclear and cytoplasmic lncRNAs. Nuclear lncRNAs are enriched for functionality involving transcriptional regulation, chromatin interactions and RNA processing. Unlike RNA located in nucleus, cytoplasmic lncRNAs are primarily engaged to improve mRNA stability and influence cellular signaling cascades (19-21). The recent study showed that some nuclear lncRNAs could also function as a ceRNA, such as NEAT1 (nuclear enriched abundant transcript 1) and MALAT1 etc. (22-24), thereby suggesting that ceRNA-associated molecular mechanisms may be much more complicated than that we thought.

LncRNAs on different malignant characters of lung cancer

Dozens of lncRNAs are implicated in different types of lung

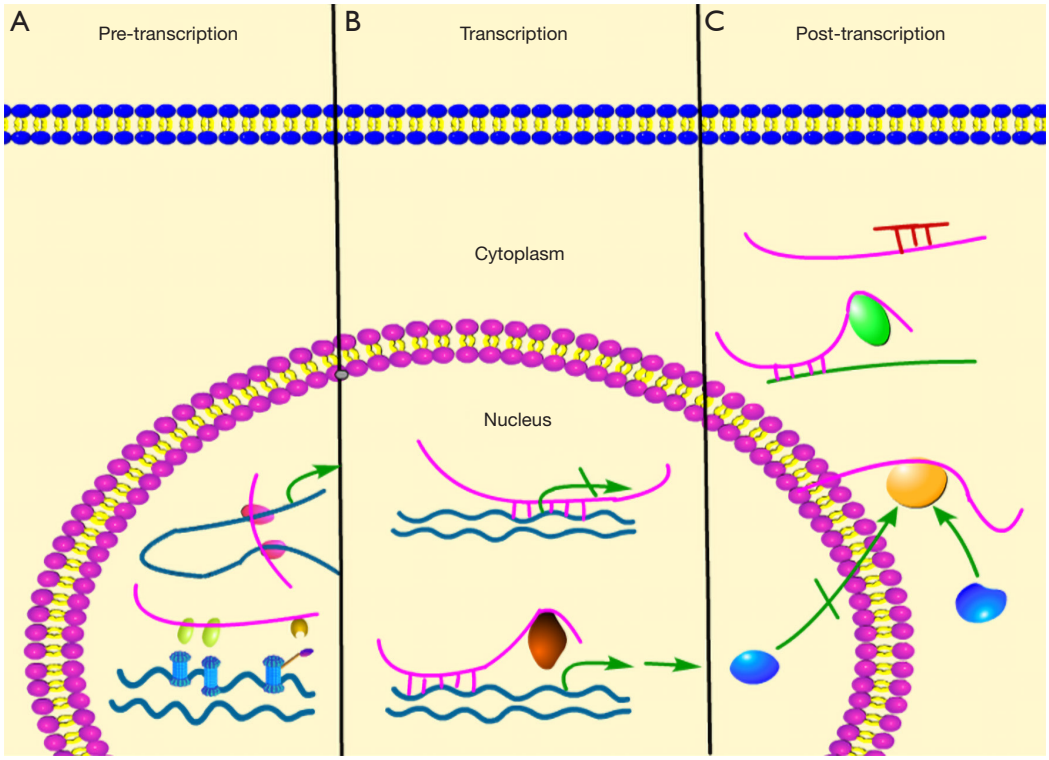

Figure 1 Biological mechanisms of lncRNAs are shown in this figure. Pink, blue, green lines stand for lncRNA, mRNA and DNA, respectively. lncRNA mechanisms can be divided into three parts. (A) At pre-transcription level, the regulation of lncRNAs associated with epigenetic regulation, involves histone modification, DNA methylation, gene imprinting, and chromosome dosage compensation. (B) At transcription level, lncRNAs can affect transcription of neighboring genes and genes on different chromosomes. Sometimes, lncRNAs may also cooperate with transcription factors to regulate the transcription of target genes. (C) At post-transcriptional level, lncRNAs always act as a ceRNA, or is engaged to modulate mRNA stability and translation, and influence cellular signaling cascades. LncRNAs' functions lie on their subcellular localization. Nuclear lncRNAs mainly functions in pre-transcription level and transcription level regulation, while cytoplasmic lncRNAs are involved in post-transcription regulation.

Table 1 Lung cancer-associated lncRNAs

LncRNAs	Alterations	Lung cancer phenotypes	Function in lung cancer	References
AFAP1-AS1	Upregulated	Invasion and metastasis	Promoting	(25)
AC006050.3-003	Upregulated	Drug-resistance	Promoting	(26)
AK126698	Downregulated	Drug-resistance	Inhibiting	(27)
BANCR	Downregulated	Invasion and metastasis	Inhibiting	(28,29)
ANRIL	Upregulated	Proliferation and apoptosis, invasion and metastasis	Promoting	(30,31)
BCYRN1	Upregulated	Invasion and metastasis	Promoting	(32)
CAR10	Upregulated	Proliferation and apoptosis	Promoting	(33)
CCAT1	Upregulated	Cancer initiation, proliferation and apoptosis, drug-resistance	Promoting	(34,35)
CCAT2	Upregulated	Proliferation and apoptosis, invasion and metastasis	Promoting	(36-38)
DLX6-AS1	Upregulated	Unexplored	Promoting	(39)

Table 1 (*continued*)

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LncRNAs	Alterations	Lung cancer phenotypes	Function in lung cancer	References
DQ786227	Upregulated	Cancer initiation	Promoting	(40)
GAS5	Downregulated	Proliferation and apoptosis, drug-resistance	Inhibiting	(41-45)
GAS6-as1	Downregulated	Unexplored	Inhibiting	(46)
GHSROS	Upregulated	Invasion and metastasis	Promoting	(47)
H19	Upregulated	Cancer initiation, proliferation and apoptosis	Promoting	(48-54)
HMlincRNA717	Downregulated	Unexplored	Inhibiting	(55)
HNF1A-AS1	Upregulated	Proliferation and apoptosis, invasion and metastasis	Promoting	(56)
HOTAIR	Upregulated	Cancer initiation, drug-resistance, proliferation and apoptosis, invasion and metastasis	Promoting	(57-64)
LINC01133	Upregulated	Proliferation and apoptosis, invasion and metastasis	Promoting	(65-67)
LINCRNA-p21	Downregulated	Proliferation and apoptosis	Inhibiting	(13,68)
lnc-bc060912	Upregulated	Proliferation and apoptosis	Promoting	(69)
loc728228	Upregulated	Proliferation and apoptosis, invasion and metastasis	Promoting	(70)
LUADT1	Upregulated	Proliferation and apoptosis	Promoting	(71)
MALAT1	Upregulated	Invasion and metastasis	Promoting	(72-80)
MEG3	Downregulated	Cancer initiation, proliferation and apoptosis, drug-resistance	Inhibiting	(81-83)
LINC00115	Upregulated	Unexplored	Unexplored	(84)
MIAT1	Upregulated	Unexplored	Unexplored	(84)
MVIH	Upregulated	Proliferation and apoptosis, invasion and metastasis	Promoting	(85)
NEAT1	Upregulated	Proliferation and apoptosis, drug-resistance	Promoting	(86,87)
NKX2-1-AS1	Upregulated	Proliferation and apoptosis	Promoting	(88)
PANDAR	Downregulated	Proliferation and apoptosis	Inhibiting	(89)
DRAIC	Downregulated	Invasion and metastasis	Inhibiting	(90)
PVT1	Upregulated	Proliferation and apoptosis, invasion and metastasis	Promoting	(91,92)
RGMB-AS1	Upregulated	Proliferation and apoptosis, invasion and metastasis	Promoting	(93)
SCAL1	Upregulated	Proliferation and apoptosis, anti-cytotoxic effect	Promoting	(94,95)
SOX2-OT	Upregulated	Proliferation and apoptosis	Promoting	(96)
SPRY4-IT1	Upregulated	Invasion and metastasis	Promoting	(97)
TUG1	Downregulated	Proliferation and apoptosis	Inhibiting	(98)
ZXF1	Upregulated	Invasion and metastasis	Promoting	(99)
lncRNA-LET	Downregulated	Invasion and metastasis	Inhibiting	(100)
UCA1	Upregulated	Drug-resistance	Promoting	(101)
XIST	Upregulated	Invasion and metastasis	Promoting	(102)

cancer (*Table 1*). From the table we can see that most of these lncRNAs function as cancer promoters. Furthermore, all the oncogenic lncRNAs are upregulated in lung cancer, while tumor-inhibiting ones are downregulated. Several lncRNAs have been well characterized to be involved in cancer initiation and metastasis, insensitivity of patients to chemotherapeutic compounds, radiations and targeted therapy, and the proliferation, apoptosis and invasion in lung cancer cells, while the biological functions of several lncRNAs remain to be further explored in lung cancer, including LINC00115, MIAT, HMlincRNA717, GAS6-as1 and DLX6-AS1 (39,46,55,84). Additionally, one lncRNA can exert multiple functions in different cancers. These lung-cancer-associated lncRNAs were subsequently summarized according to their biological functions.

LncRNAs associated with lung cancer initiation

The mechanism of cancer initiation is always of great importance for the study on lung cancer, but is still far from complete understanding. Identification of the relevant players in the process of malignant transformation is a key step to Cancer Res. Previous studies show that 5 lncRNAs can induce malignant transforming of lung and human bronchial epithelial (HBE) cells under specific condition.

H19 is the first lncRNA discovered in human cells and highly expressed during the development of the embryo and fetus, while it is shut down in most tissues shortly after birth (103). Interestingly, this molecule was initially described as an anti-tumor molecule, but the most recent studies have demonstrated that H19 exerts an oncogenic function in various malignancies including lung, breast, cervix, esophageal, ovarian, bone and bladder cancers (54,104-110). Some studies have suggested a distinctive function of H19 in the initiation of lung cancer. Kaplan *et al.* reported that loss of imprinting (LOI)-caused H19 overexpression acted as one of early markers in the progression of airway epithelium malignant transformation. They found that H19 presented a high expression level in airway epithelium of smokers without alterations of other imprinted genes. Then, they treated HBE cells with cigarette smoke exposure (CSE) and found that a significant increase in H19 level was followed by malignant transformation (48). Another study by Hu *et al.* reported that HBE cells induced by cigarette smoke condensate showed a significant alteration in transcription profile of cancer-associated genes, including H19, IGF2, and MEG3. This study further demonstrated that long-term treatment with cigarette smoke condensate led to malignant transformation of HEB cells (111). Expression of H19 has been revealed to be improved by mineral dust-induced gene (MDIG), and then, it leads to shortened survival of lung cancer patients and increased incidence of smokers to suffer of lung cancer. MDIG is involved in the demethylation of H3K9me3 in the promoter region of H19, and therefore, it can promote its expression (112,113). Besides the cancer-initiated function mentioned above in lung cancer, H19 has also been reported to be associated with cancer cell proliferation. As a direct transcriptional target of c-Myc, H19 knockdown significantly inhibits NSCLC cell proliferation both *in vitro* and *in vivo* (50-52). LncRNA maternally expressed gene 3 (MEG3), a tumor-inhibiting molecule, has also been reported to be associated with various types of tumor tissues and cell lines. Different from H19, MEG3 exerts a distinctively anti-malignant-transformed function in lung carcinoma. MEG3 downregulation is attributed to environmental carcinogennickel-induced DNA methyltransferase 3b (DNMT3b) upregulation in HBE cells. Downregulation of MEG3 contributes to malignant transformation via reducing its binding to transcription factor c-Jun, an inhibitor of PHLPP1. The further study showed that decreased PHLPP1 can lead to Akt/p70S6K/S6 pathway activation, thereby increased the expression of HIF-1α and malignant transformation in HBE cells (81). This study indicates a unique anti-malignant-transformed function of MEG3 in lung cancer. CCAT1 (Colon cancer associated transcript 1, CARLo-5) was first found to be upregulated in colon carcinoma, and it has been reported to be downregulated in various cancers, including lung carcinoma (114-118). CCAT1 is mainly associated with malignant transformation of lung cancer. Lu *et al.* reported that CCAT1 functioned as a ceRNA to inhibit miRNA let-7, and then, it induced a malignant transformation through indirectly promoting activity of c-Myc in CSE-induced HBE cells (34). In a lncRNA expression microarray analysis, Gao *et al.* reported a lncRNADQ786227, which was found to be overexpressed in benzo(a)pyrene-induced HBE cells and it induced malignant transforming. According to the study, DQ786227 is upregulated in transformed HBE cells. Further studies on lncRNA DQ786227 is required (40).

LncRNAs on tumor cell proliferation and apoptosis

The uncontrollable cell proliferation and apoptosis is one of the most common malignant characters of cancer. There are

23 known lncRNAs which are associated with lung cancer cells proliferation and apoptosis, such as ANRIL, HOTAIR and lincRNA-p21 etc. In this part, several important proliferation-and-apoptosis-associated lncRNAs and their underlying mechanisms in lung cancer are summarized, and the others can be seen in *Table 1*.

ANRIL (antisense non-coding RNA in the INK4 locus) was first uncovered in a genetic analysis of patients (119). It is reported that ANRIL functions as a promoter of cell proliferation in lung cancer. With the loss-of-function study, Nie *et al.* showed that ANRIL (mostly located in the nucleus) affected lung cancer cell proliferation and apoptosis partly via enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2)-dependent silencing of Kruppel like factor 2 (KLF2) and p21 transcription (30). Another study revealed that ANRIL is transactivated by c-Myc (31). Apoptosis-regulated lncRNA, lincRNA-p21, acts as a repressor in p53-dependenttranscriptional responses. The inhibition of this lncRNA affects expressions of hundreds of gene targets enriched for genes normally repressed by p53 in lung cancer cells. It was reported that this effect was mediated via a physical association with hnRNP-K (13). Up to now, the function of lincRNA-p21 as a promoter of cancer cell apoptosis has been reported in several malignancies, including prostate, hepatocellular and colorectal cancer (68,120-123). Recently, Thai *et al.* identified a novel cancer-inhibiting lncRNA, SCAL1 (the smoke and cancer–associated lncRNA-1), which is upregulated in the airways of smokers and various lung cancer cell lines, and transcriptionally regulated by NRF2 (nuclear factor erythroid 2-related factor). *In vitro* assays demonstrated that upregulated SCAL1 exerted an anti-cytotoxic function either in CSE-treated HBE cells or in lung cancer cells (95). Another study reported that LUCAT1 (SCAL1) was correlated to poor prognosis and promotes cell proliferation via repressing the expression of p21 and p57 in lung cancer (94). A novel lncRNA, LUADT1 (LUAD transcript 1), was reported to be highly expressed in lung cancer tissues and correlated with T staging. It functionally promotes cell proliferation in lung cancer. This lncRNA exerts cancer-promoting function via binding to proteasome component 2 (PRC2), and therefore, suppresses oncogene p21 expression (71).

LncRNAs associated with cancer invasion and metastasis

Metastasis is regarded as one of the most important lethal factors for cancer, and therefore, it is significant to explore the mechanisms of lung cancer cell invasion and metastasis for improving patients' survival. Seventeen cancer-associated lncRNAs have been revealed to be implicated in invasion and metastases in lung carcinoma (*Table 1*). In this part, several lncRNAs which exert important functions in lung cancer invasion and metastasis are introduced

Since its discovery in non-small cell lung cancer (NSCLC) (75), MALAT1 has been linked to various human malignancies, including lung, bladder, breast, colorectal, endometrial, esophageal, gastric, hepatocellular, ovarian, prostate, and renal cell carcinoma (124). MALAT1 is significantly overexpressed and can improve cancer invasion and metastasis in lung cancer (125). In lung carcinoma, it was reported that MALAT1 was regulated by transactive response DNA-binding protein-43 (TDP43) (72), Specificity protein 1 (SP1) (72), and DNA methylation (73), which played as a ceRNA through binding multiple miRNAs, such as miR-204 (74). Thus, MALAT1 regulates several EMT-associated proteins, including SLUG, TWIST and E-cadherin (126). It has also been reported that MALAT1 is associated with some other clinical parameters and malignant phenotypes in multiple malignancies. In cervical cancer cells, MALAT1 impacts cell viability, proliferation, metastasis, cell cycle progression, and tumor growth (127). In colorectal cancer, MALAT1 is correlated with the sensitivity to chemotherapy (128). These two studies indicate that there may be some uncovered associations between this lncRNA and lung cancer except for metastasis. LncRNA HOX transcript antisense RNA (HOTAIR) is a dual-located lncRNA which is located both in nucleus and cytoplasm (72). It has been reported that the elevated expression of HOTAIR is associated with cell proliferation, migration and invasion in pancreatic, prostate, gastric, colorectal, cancer and melanoma (73,74,126-128). While the main function of HOTAIR in lung carcinoma refers to invasion and metastasis. In lung carcinoma, HOTAIR level is always accompanied by advanced stages, metastases, and shortened patient survivals in lung malignant disease (29,129). By means of supporting a role for HOTAIR in lung cancer metastasis, siRNA-mediated downregulation of this lncRNA decreased the migration and invasion of lung cancer cells *in vitro* and their metastatic potential *in vivo* (28). The further study showed that HOTAIR regulated the ratio of FoxA1 to FoxA2 via interacting with chromatin remodeling factor LSH, thereby affecting invasive and metastatic phenotypes of lung cancer cells (130). It has also been indicated that HOTAIR is associated with lung malignant transformation. HOTAIR promotes malignant

transformation process via activating autocrine IL-6/STAT3 signaling in cigarette smoke extract (CSE)-treated HBE cells (131). Another metastasis-associated lncRNA BANCR (BRAF-regulated lncRNA1), which is induced by oncogene $BRAF^{V600E}$ (129), functions via suppressing MAPK signaling and then inhibiting the transcription of EMT-related proteins in lung carcinoma (28,29). It has also been revealed that BANCR exerted an anti-tumor function to suppress cell invasion and metastasis in colorectal, thyroid, bladder cancer and melanoma (130-133). LncRNA-LET has been shown to be a tumor suppressor in various malignancies. In nasopharyngeal carcinoma, it has been revealed that a significant downregulated level of lncRNA-LET is regulated by EZH2-mediated H3K27 histone methylation (134). The tumor-suppressive function of LET has been reported in gallbladder and gastric cancer (135,136). The hypoxia-induced histone deacetylase 3 suppresses the expression of lncRNA-LET by affecting its promoter, and it eventually facilitates NF90 accumulation and hypoxia-induced cell invasion in lung cancer (100). This finding suggests a lncRNA-mediated connection between metastasis and hypoxia. Recently, Sakurai *et al.* reported a novel lncRNA downregulated RNA in androgen independent cells (DRAIC), which is downregulated in lung cancer, acts as an anti-tumor player. Overexpression of DRAIC significantly represses cell migration and invasion in lung cancer (90).

LncRNAs involved in therapy-resistant effects

Chemotherapy and radiotherapy are both important modalities against malignancies. However, resistance of cancer cells remains an impediment to the therapeutics. In this part, 8 lncRNAs which increase or decrease therapy-resistant of lung cancer patients are summarized.

Growth arrest-specific transcript 5 (GAS5) is a well-known anti-tumor lncRNA associated with cancer cell apoptosis. It mainly affects sensitivity of chemotherapy in lung carcinoma. Zhang *et al.* reported that GAS5 can enhance cisplatin sensitivity in lung cancer via autophagy inhibition (137). Another study demonstrated that GAS5 can promote gefitinib-induced lung cancer cell death through inhibiting IGF-1R expression (45). It is revealed by Xue *et al.* that GAS5 enhanced radiosensitivity through interacting with miR-135b in lung cancer cells (42). Moreover, Xia *et al.* showed that MEG3 functioned as increasing cisplatin sensitivity of lung cancer cells through regulation of p53, β-catenin and surviving (83). One study on NEAT1 in lung cancer revealed that the interaction between NEAT1 and CTR1 (Copper transporter 1) promoted the internalization of a significant fraction of cDDP (Platinum-based chemotherapy, such as cisplatin) in tumor cells, thereby enhancing cisplatin sensitivity (87). LncRNA HOTAIR has been well demonstrated to be implicated in multiple aspects of malignant characters, including drug-resistance. Fang *et al.* found that downregulation of HOTAIR can promote cell sensitivity to anti-cancer drugs, thus suppressing cell viability, cell cycle arrest, and tumor growth (63). Except for its role in drug-resistance, a study on HOTAIR reported that over-expression of this lncRNA decreased radio-sensitivity via inactivating β-catenin (64). Additionally, Hou *et al.* found that a lncRNA, AC006050.3-003, can potentially play a key role in chemo-resistance (26). Yang *et al.* reported that AK126698 appeared to induce cisplatin resistance by targeting the Wnt pathway in lung cancer cells (27). Urothelial cancer-associated 1 (UCA1) was previously reported to downregulate and exert its oncogenic function in bladder and hepatocellular carcinoma (138,139). Cheng *et al.* revealed that this molecule was upregulated to induce cancer cell acquired resistances to EGFR-TKIs (epidermal growth factor receptor tyrosine kinase inhibitors) through activating AKT/mTOR pathway (101).

Lung cancer lncRNAs functionally distinct from other malignancies

According to previous researches, the biological functions of several specific lncRNAs in lung cancer are always distinguished from other human malignant tumors, through affecting different signaling pathways. In this part, two unique lncRNAs in lung cancer (PANDAR and TUG1) were mainly discussed with comparing to multiple malignancies (*Figure 2*).

It was reported that the lncRNA promoter of CDKN1Aantisense DNA damage-activated RNA (PANDAR) was induced by DNA damage, and then, it functionally regulated the proliferation and apoptosis of cancer cells (140). According to previous studies, this lncRNA is overexpressed in tumor tissue, and then, boost cell proliferation or metastasis in most malignancies, except for lung carcinoma. In liver cancer, it was reported that PANDAR was overexpressed in cancer cells and associated with poor prognosis. Silencing of PANDAR represses cell proliferation, colony formation and cycle progression (141). In colorectal cancer, PANDAR functions as an independent prognostic factor which correlated to tumor size and prognosis of patients, and its overexpression promotes EMT of cancer cells (142). Besides,

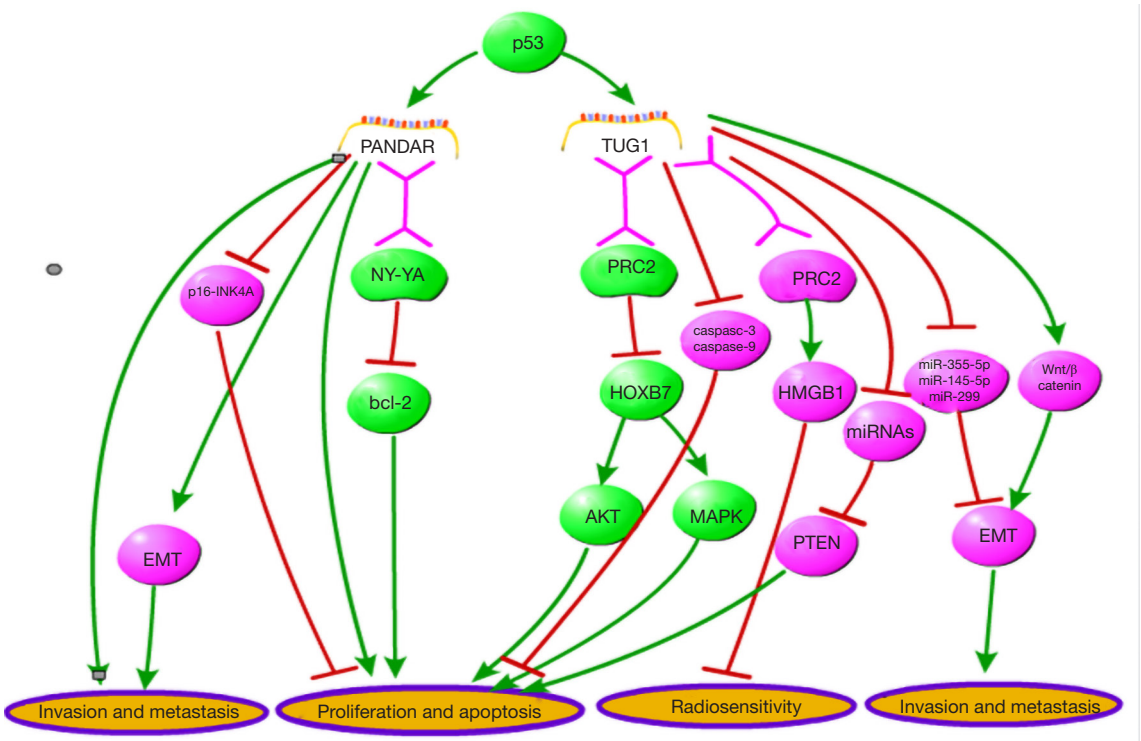

Figure 2 The known functions and mechanisms of two special lung cancer lncRNAs, TUG1 and PANDAR, are demonstrated in this figure. Green lines stand for the molecular interaction specific for lung carcinoma, while red lines stand for the common pathways that mediate the action of TUG1 and PANDAR in other cancers. These two lncRNAs function as cancer inhibitors in lung carcinoma. The unique cancer-inhibiting functions of TUG1 and PANDAR are both mediated by RNA binding proteins, and regulated by p53 in lung cancer, while their p53-dependent anti-tumor mechanism has not been reported to be involved in other malignancies.

it has been reported that PANDAR expression is positively correlated with advanced stages and poor prognosis in bladder cancer. Suppression of this lncRNA decreased invasion and metastasis, and increased apoptosis in bladder cancer cells (143). Additionally, it has been reported that PANDAR is upregulated and it facilitates cell proliferation in breast cancer. Knockdown of PANDAR inhibits G1/S transition of breast cancer cells via suppressing $p16^{INK4A}$ (144). In gastric cancer, it has been demonstrated that PANDAR was highly expressed in cancerous tissues, which is positively correlated to tumor size, lymph node burden and lower survival rates (145). Moreover, Wu *et al.* has showed an early-stage diagnosis value of circulating PANDAR in clear cell renal cell carcinoma (146). The expression profile and function of PANDAR is completely different in lung carcinoma from other cancers mentioned above, although it is consistently upregulated in cancer and functions as a cancer promoter in most malignancies. Han *et al.* reported that PANDER exhibited a downregulated expression level in lung cancer and was negatively associated with tumor size and TNM stages. Furthermore, PANDAR was found to be regulated by p53. Upregulation of PANDAR inhibits Bcl-2 expression via interacting with RNA binding protein NY-YA, thus, functionally inhibiting cell growth *in vitro* and *in vivo* (89).

LncRNA TUG1 (taurine upregulated gene1) was firstly reported to be upregulated in taurine-treated mouse retinal cells and associated with retinal development (147). Since Khalil *et al.* revealed its function of recruiting PRC2 via genome-wide RNA immune precipitation (148), TUG1 has been demonstrated to be associated with several malignant diseases. The same as PANDAR, the expression and function of TUG1 in lung carcinoma is also opposite to other cancers. According to a study on colorectal cancer, an elevated expression level of TUG1 was detected in tumor tissues and associated with metastasis phenotype of tumor cells (149). Wang *et al.* demonstrated that TUG1 functions as a ceRNA to regulate miRNA-355-5p, thereby promoting migration and invasion in osteosarcoma cells (150).

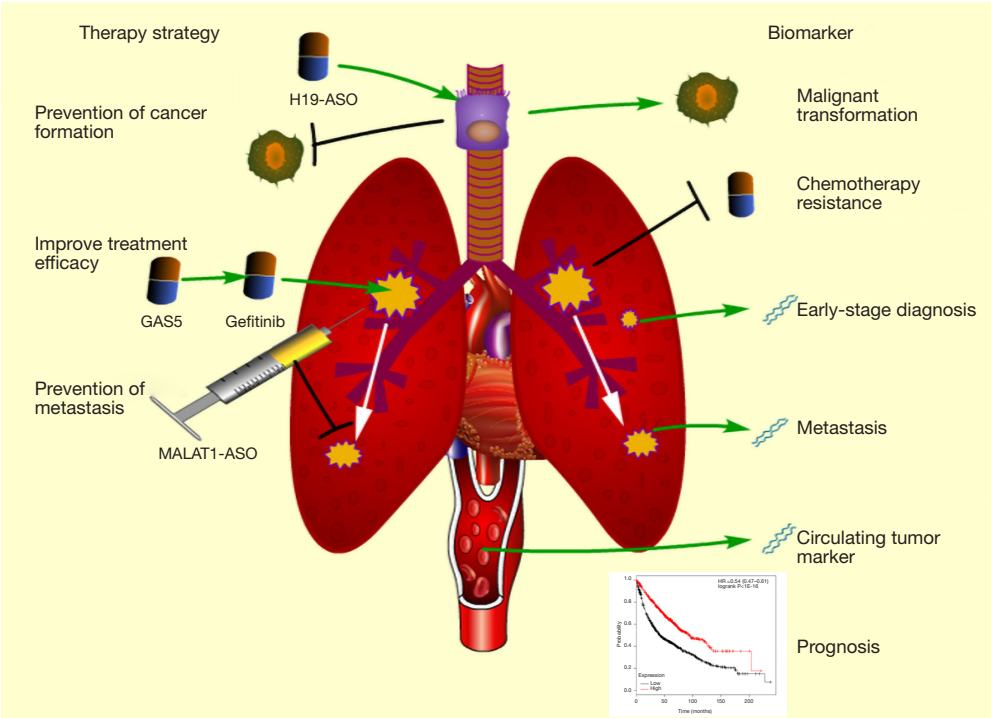

Figure 3 The potential clinical applications of lncRNAs are demonstrated in this figure. The items in the left stand for lncRNAs' potential in lung cancer prevention and treatment; right ones stand for the potential applications in prediction, diagnosis and prognosis of lung cancer.

Moreover, Jiang *et al.* revealed that TUG1 decreases radiosensitivity in bladder carcinoma via regulating the expression of HMGB1 (high mobility group box 1 protein), a chromosome-binding protein associated with DNA repair, duplication, transcription, and nucleosome packaging (151). Additionally, the function of promoting cell metastasis in TUG1 has also been reported in breast cancer, gastric cancer, endometrial cancer, small cell lung cancer and other malignancies (152-157). Unlike the tumorigenic role in other the above-mentioned cancers, TUG1 exerts a distinctively tumor-inhibiting function in NSCLC. Recently, Zhang *et al.* demonstrated that TUG1 is downregulated and functions as a cancer inhibitor in lung carcinoma. Through univariate and multivariate analyses in a cohort of 192 lung cancer patients, it was revealed that TUG1expression was negatively associated with TNM stage, tumor size, and shortened overall survival in lung cancer. Furthermore, this study showed that TUG1 is regulated by p53 via directly regulating its transcription. They also found that TUG1 inhibits cell proliferation via PRC2-mediated inhibiting of homeobox B7 (HOXB7), thus affecting AKT and AMPK pathways. The p53/TUG1/PRC2/HOXB7 axis reveals a distinctive anti-tumor function of TUG1 in lung carcinoma. The anti-tumor function of TUG1 in lung cancer has also been certified in another study (98,158).

These above studies showed that the role of lncRNA may be not consistent in different types of malignancies. The unique cancer-inhibiting functions of TUG1 and PANDAR are both mediated by RNA binding proteins, and regulated by p53 in lung cancer. The p53-dependent mechanisms have not been revealed in other malignant diseases yet. This unique mechanism of the two lncRNAs' function may be associated with some molecular features specific for lung carcinoma. Thus, it is instrumental in improving lung cancer therapy to further elucidate the molecular mechanism of lung cancer specific lncRNAs.

Potential clinical applications of lung cancer-related lncRNAs

In addition to their roles in diseases, accumulated references suggest that lncRNAs obtained from either blood, tissue, or exhaled breath may provide reliable biomarkers for the diagnosis and prognosis of lung cancer. Moreover, the potential of lncRNAs on cancer therapy remains to be developed (*Figure 3*).

Biomarkers for prediction, diagnosis and prognosis

It has been demonstrated that smoking is correlated to the incidence of lung cancer (159,160). As mentioned above, the expression levels of H19 and MEG3 are significantly increased and decreased in CSE-treated bronchial epithelial cells respectively, and these two lncRNAs have critical functions in malignant transformation. Besides, it has been also revealed that HOTAIR and DQ786227 are associated with lung cancer initiation. Thus, it is significant for long-term smokers to screen the expression level of these lncRNAs in their bronchial epithelial cells to evaluate the incidence of lung cancer. This screening can be accomplished with their bronchial washing fluids or bronchial epithelial cells during bronchoscopy. Additionally, for better clinical application, it is necessary to define the threshold concentrations of these lncRNA biomarkers for lung cancer prediction.

The intraoperative pathological diagnosis is a main approach to differentiate benign and malignant tumors (161). Since it is difficult to detect these cancer cells in some early-stage cases, more biomarkers are required for the diagnosis of lung cancer. Some lncRNAs (H19, MALAT1, HOTAIR, etc.) always significantly are overexpressed in early stage of lung cancer (50,60,78). Thus, the detection of these lncRNAs can provide us with an approach to timely detect pulmonary malignant tumors. Furthermore, circulating lncRNAs can be used in auxiliary lung cancer diagnosis. It has been reported that both GAS5 and MALAT1 can exhibit elevated expression levels in whole blood of early-stage lung cancer patients (162,163). Screening of MALAT1 and GAS5 in blood is significant for diagnosis of early-stage lung cancer.

Chemotherapy is one of primary therapeutic strategies against malignancies. According to previous studies, the overexpression of these chemotherapy-resistance-associated lncRNAs (GAS5, NEAT1, UCA1, etc.) can affect therapeutic effect of chemotherapy. In order to improve the efficacy, it is highly required to screen on chemotherapy-resistance-associated lncRNAs in lung tumor. In order to obtain necessary biological information for postoperative chemotherapy, it is of important clinical significance to detect these lncRNAs in intraoperative pathological tissue. Unlike the patients who are undergoing surgery, the detection of predictive lncRNA can be performed for these preoperative or non-operative patients during CT-guided percutaneous biopsy.

The invasion and metastasis are closely related to prognosis of lung cancer patients (164). MALAT1 is overexpressed in lung cancer tissues, as well as circulating system, and plays a critical role in lung cancer metastasis (80,163,165). High MALAT1 level in intraoperative pathological tissues or in whole blood indicated a metastatic potential for patients with lung carcinoma.

In addition, it has been reported that several lncRNAs are associated with prognosis of lung cancer patients (60,67,78,162,165-168). With the help of available big data, such as The Cancer Genome Atlas (TCGA), we can identify multifactor prognostic markers through analyzing the correlation between lncRNA expression and survival rate. It is more likely to achieve a more precise prognosis through a combined application of these lncRNA biomarkers for lung cancer patients.

Potentially therapeutic applications

The molecule-targeted therapy is a novel and potential approach against malignancies featured with better outcomes and fewer side effects. Several lung-cancer-associated lncRNAs are critical for initiation, progression, and metastasis of lung cancer, thus having potential to act as therapeutic targets. Theoretically, the regulation of expression of these target lncRNAs can prevent the initiation of lung carcinoma and decrease the malignancy of tumor cells. Antisense oligonucleotides (ASOs) are short single-stranded deoxyribonucleotide analogs, which can downregulate RNAs via binding their complementary sequence. One study has demonstrated that injection of MALAT1-specific ASO into lung tumor can significantly inhibit lung cancer metastasis (79). Maybe, similar approaches can also be used to silence H19, which is elevated in SCE-treated bronchial epithelial cells and induces lung cancer initiation as mentioned above, to prevent the formation of lung carcinoma induced by smoking. Regarding that MEG3 can prevent malignant transformation in bronchial epithelial cells (81), it is possible to prevent lung cancer through the restoration of MEG3 in human lung and bronchial epithelial cells with effective transfer vectors. In addition, lncRNAs involved in chemotherapy sensitivity can improve therapeutic effect of drugs on lung cancer. As noted above, HOTAIR can reduce the sensitivity of lung carcinoma cells to chemotherapeutic drugs, such as cisplatin (63). Theoretically, the cisplatin effect can be improved by treatment of lung cancer patients with HOTAIR-specific ASO. Moreover, several lncRNAs can also be used for the enhancement of chemotherapy,

including UCA1, NEAT1 and GAS5.

Discussion

Although numerous studies have reported that many lncRNAs are closely associated with lung cancer, the functions and clinical potential of these lncRNAs are far from being well-understood. Tumor-derived lncRNAs are not suitable to widely and clinically predict the progression of lung cancer due to its relatively low accessibility, while lncRNAs in blood are more valuable in lung cancer diagnosis and prognosis prediction. Therefore, it is urgently needed to study circulating lncRNAs more intensely for future clinical application. The uncontrollable recurrence and metastasis are the highest lethality factors for lung cancer patients, as well as other malignancies, and however, it is yet to report which lncRNAs are correlated to cancer recurrence. Additionally, it has been revealed that several cancer-inhibiting lncRNAs are implicated in lung cancer, such as MEG3, PANDAR, DRAIC. It is promising to further develop anti-tumor therapeutic strategies based on utilizing these tumor suppressor lncRNAs.

Up to now, several miRNAs, like miR-34, have been well-studied, and ready to be used for diagnosis and therapy of malignancies (169), while lncRNA-based therapeutics are still far from clinical applications. Some problems are needed to be solved to facilitate the clinical application of lncRNAs, such as safety of lncRNA-based drugs, and delivery of therapeutic agent into target cells.

Circular RNAs represent a novel class of endogenous RNAs with diversity and universality (170). Recent studies have well demonstrated the relationship between circular and linear RNAs and the possible mechanisms of cyclization (171,172), thus implying that lncRNAs may transform from linear form into circular one. For instance, the cyclization of ANRIL is induced by Alu repeats flanking its exons, and exerts different functions from linear ANRIL (173). Therefore, the emerging of circular RNA provides a new direction for lncRNAs' study.

Conclusions

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.10.22). The authors have no conflicts of interest to declare.

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