Review

Diagnostic and Prognostic Potential of Circulating Long Non-Coding RNAs in Non Small Cell Lung Cancer

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Key Words

Lung cancer • Long non-coding RNAs • Biomarker

Abstract

Lung cancer is the leading cause of cancer-related mortality worldwide. Approximately 80% of lung cancer cases are non-small cell lung carcinoma (NSCLC). However current diagnostic and therapeutic modalities against NSCLC are ineffective due to incomplete understanding of molecular pathogenesis of NSCLC. Emerging evidence shows that long non-coding RNAs (lncRNAs) can function as biomarkers for diagnosis and prognosis. lncRNAs can control transcription, translation, and protein function via diverse mechanisms although they lack the protein coding potential. lncRNAs have attracted intense investigations on their roles in cancer. Mounting evidence indicates that lncRNAs are promising biomarkers in diagnosis and prognosis for NSCLC, especially their presence in body fluids. Herein we will review recent advances in the research that explores the diagnostic and prognostic potentials of lncRNAs in NSCLC. We will also discuss emerging evidence that suggested lncRNAs as therapeutic targets in NSCLC.

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Introduction

Lung cancer is the most common cancer among men and women and leading cause of cancer related morbidity and mortality worldwide. Due to environmental pollution, it is estimated that more than 2.2 million people were newly diagnosed and approximately 1.5 million people died from this disease in 2017 [1]. Non-small cell lung carcinoma (NSCLC) accounts for 80% of total lung cancer cases and is divided into three histological types,

namely lung adenocarcinoma, large cell carcinoma, and lung squamous cell carcinoma. Different histological types respond differently to chemotherapies [2-5]. A minor histological type is adenosquamous carcinoma that accounts for 0.6-2.3% of lung cancer and is often misdiagnosed as adenocarcinoma or squamous cell carcinoma due to its mixed clinical and pathological characteristics.

Lung adenocarcinoma is the most common histological type. There are many studies on targeted therapy of lung adenocarcinoma, such as tyrosine kinase inhibitors (TKIs) of the epidermal growth factor receptor (EGFR) [6]. The patients who are initially responsive to TKIs usually develop drug resistance in 8-12 months after initiation of their TKI target therapy [7]. Resistance to TKI target therapy has been under intense investigation.

Current Diagnostic Method for Lung Cancer

Pathological diagnosis is the gold standard in clinic setting. Chest radiograph has been used to screen for lung cancer for the past two decades, but its false negative rate is high [8]. Low dose spiral computed tomography(CT) was developed to increase sensitivity of screen for lung cancer [9]. A recent advance is fluorodeoxy glucose-positive emissiontomography (FDG-PET) scan that substantially increases specificity and sensitivity when compared to the previous methods [10-12]. Circulating tumor cells (CTCs) [13], tumor-educated platelets [14] and tumor-associated autoantibodies (TAAbs) [15] also emerge as promising methods for screening of NSCLC. lncRNAs have emerged as a new class of biomarkers for diagnosis and prognosis of NSCLC. Microarray and genomewide deep sequencing can reveal specific lncRNAs and their potential functions in NSCLC subtypes [16].

Brief introduction of Long non-coding RNAs

lncRNAs are a class of non-coding RNAs that are longer than 200 nucleotides in length and lack the protein coding potential [17]. Recently, Iyer et al. demonstrated that there are about 60000 ncRNAs in the human genome and more than 70% of these are lncRNAs [18]. About 80% of lncRNAs are not annotated. lncRNAs can regulate biological processes via diverse molecular mechanisms, such as decoys, scaffold, signal transducer, sponges for miRNAs, and a guide for chromatin modifiers [19, 20].

Biological functions of lncRNAs

A large number of lncRNAs regulate the expression protein-coding genes via *in cis* (affecting neighboring genes) or *in trans* (affecting distant genes on different chromosomes) mechanisms [21, 22]. Various lncRNAs have been reported to regulate individual genes and gene expression programs through epigenetic regulation or by altering the basal transcriptional machinery. Specifically, lncRNAs can (1) regulate the downstream genes' transcription; (2) regulate mRNA splicing patterns and produce different splice variants; (3) modulate protein's activity; (4) scaffolds for assembly of multiple component complexes; (5) regulate proteins' subcellular localization; (6) function as transcriptional precursors of small RNAs [23]. It is conceivable that aberrant expression of lncRNAs results in dysregulation of normal biological and pathological processes and thereby contributes to the pathogenesis of disease [24]. Utilizing comparative mammalian genomics approach coupled with evolutionary analysis, Khachane and Harrison identified a small population of conserved lncRNAs in the evolution, and proposed that these lncRNAs could play an important role in tumorigenesis [25]. A large number of lncRNAs exhibit altered expression in cancer cells compared with healthy tissue of the same origin [26, 27].

lncRNA in lung cancer diagnosis and tumor types

The diagnosis of lung cancer largely relies on tissue biopsy. However it has considerable limitations, such as small amount of tissue extracted and complication derived from necrotic tissues within tumors. Because of the tumor heterogeneity, adenocarcinoma and squamous cell carcinoma can exist in the same tumor. So, there is a possibility that an adenosquamous carcinoma is misdiagnosed as adenocarcinoma or squamous cell carcinoma [28-30]. Increasing number of lncRNAs are associated with lung adenocarcinoma (LUAD), lung squamous cell cancer (LSCC), etc [31]. lncRNAs bear the potential as a new category of biomarkers for diagnosis of NSCLC.

Using qRT-PCR, RNA-SEQ and the TCGA dataset, Tian and his colleges [32] aimed to generate a histopathology relevant lncRNAs for scanning of functional lncRNAs in 6 TNM I stage (stage I) LUAD. They found that the expression of LINC00963, NR2F2-AS1, LINC00515, LINC00162, LINC00312, MGC27382, LINC00472 and FENDRR were significantly dysregulated in LUAD tissues. CDKN2B-AS1 was significantly up-regulated in our analysis of the TCGA RNA-SEQ dataset, and its upregulation was confirmed in our cohort using qRT-PCR. However it is noteworthy that discrepancy between the TCGA RNA-SEQ data and qRT-PCR for an individual lncRNA. For instance, MINCR and LBX2-AS1 were up-regulated in RNA-sequencing and TCGA dataset, while the results of qRT-PCR showed down-regulation of both lncRNAs. HNF1A-AS1 was significantly down-regulated in RNA-sequencing and qRT-PCR, but was up-regulated in TCGA dataset [32].

SPRY4-IT1 is an lncRNA that has been widely reported in many human cancer types. Zhang et al. found SPRY4-IT1 was significantly up-regulated in LUAD tissues (not in LSCC) and further analysis show that the LUAD patients with high SPRY4-IT1 expression exhibit significantly poorer overall survival than those patients with low SPRY4-IT1 expression [33].

Liu et al. found IGF2BP2-AS1 and DGCR5 correlated with better OS in LSCC, while MIR31HG, CDKN2A-AS1 and LINC01600 predicted poor OS in LUAD [34].

Li [35] and Wang [36] separately found that high expression of RGMB-AS1 and LINC01207 in LUAD is associated with a poor prognosis.

LCAL6 (also named as BLACAT1) was higher in LUAD than LSCC ($P = 0.014$) and correlated with larger tumor size and poor survival of LUAD patients [37].

In addition XLOC_008466, FAL1, and XIST were examined in NSCLC by Yang [38], Pan [39] and Wang, [40], respectively. In their studies, these lncRNA function as an oncogene in NSCLC, which indicates them as a useful marker and potential therapeutic target.

With the help of microarrays from the Gene expression omnibus database and bioinformatics analyses, Wang et al. [41] found LINC00342 is significantly up-regulated in NSCLC and is potentially a prognostic biomarker.

Analysis of Whole Blood, Serum and Plasma

Whole Blood and lncRNA Profiling

Only three studies reported lncRNA's expression in whole blood samples. All of the studies used either RT-PCR or qRT-PCR to measure lncRNA, allowing comparisons to be made between them. Thai P [42] found that the lncRNA SCAL1 was elevated in the airways of smokers and in many lung cancer cell lines. Moreover the expression SCAL1 is regulated by NRF2 that is reported to mediate protection against cigarette smoke-induced toxicity [43]. MALAT1 is another important lncRNA in lung cancer's progression. Many studies showed that MALAT1 was upregulated in tumor tissues when compared with the normal lung tissues [44-46]. But Guo [47] and Weber DG [48] found that the whole blood expression of MALAT1 was lower in the patients with NSCLC than normal people. Comparable results were reported by Zhang et al., the expression of MALAT1 were downregulated in hepatocellular carcinomas patients [49]. Researchers propose that MALAT1 is expressed ubiquitously but its tissue-specific functions depend on the cellular environment [50]. Wu and his colleges [51]

reported that the level of a novel lncRNA NR-026689 is significantly increased in whole blood of lung cancer in rat and human lung cancer cell lines. These three lncRNA -SCAL1, MALAT1 and lncRNA NR-026689, can be used as biomarkers in bodyfluids for early detection of lung cancer. We summarize these lncRNAs in Table 1.

lncRNA Profiling in Serum

A positive correlation between lncRNA loc146880 expression and lc3b levels in tumor tissues and serum of lung cancer patients was reported by Deng and his colleagues [52]. Another scientist Tantai

[53] reported that the levels of XIST and HIF1A-AS1 were significantly increased in tumor tissues or serum from NSCLC patients. Moreover, serum levels of XIST and HIF1A-AS1 were significantly decreased after surgical resection of tumors (tumor load reduction) as compared to the pre-operative stage. Combined tissue and serum results, Xie's [54] study demonstrated that lncRNA SOX2OT and ANRIL might be ideal biomarkers for NSCLC diagnosis and prognosis. We summarize these lncRNAs in Table 2.

lncRNA Profiling in Plasma

Early diagnosis of lung cancer can greatly reduce mortality. However, a lack of suitable plasma biomarkers presents a major obstacle. Zhu H reported that lncRNA16 (ENST00000539303) expression was significantly higher in plasma of lung cancer patients ($p < 0.05$) [55]. His findings suggest that lncRNA16 is a biomarker for early diagnosis and a potential therapeutic target. In Liang's report [56], the lncRNA growth arrest-specific transcript 5 (GAS5) also appears to be a promising biomarker for early diagnosis of NSCLC. The plasma levels of GAS5 were significantly lower in NSCLC patients compared with healthy controls. Moreover, Wang H M, et al. [57] demonstrated that lncRNA-UCA1's expression was significantly increased in plasma from NSCLC patients, and the expression in plasma and tumor tissues were strongly correlated in 60 patient samples. Hu et al. hold the opinion that the plasma lncRNA acting as fingerprint in non-small-cell lung cancer, he found Circulating SPRY4-IT1, ANRIL, and NEAT1 were significantly increased in plasma samples and might serve as signature for the prediction of NSCLC [58]. Tang et al. [59] discovered that three lncRNAs (RP11-397D12.4, AC007403.1, and ERICH1-AS1) were up regulated in NSCLC patients plasma, which indicates potential biomarkers for predicting the tumorigenesis of NSCLC. We summarize these lncRNAs in Table 3.

lncRNA Profiling in Sputum

Lung cancer is a heterogeneous disease featuring field defects in the airway [60]. Most lung cancer patients present the symptoms of cough and expectoration. Sputum is widely collected in clinical work, so biomarkers in sputum can be used for early detect lung cancer. But at present, there is no lung cancer-related lncRNAs detected in sputum. However several

Table 1. lncRNAs as biomarkers in lung cancer' whole blood

lncRNA	Function	Function	Sample	References
lncRNA SCAL1(up)	Diagnostic	Lung cancer patients vs healthy controls	Whole blood	[42]
lncRNA MALAT1(down)	Diagnostic	NSCLC patients vs. healthy controls	Whole blood	[47, 48]
lncRNA MALAT1(up)	Diagnostic and Prognostic	NSCLC patients vs. Controls	tissue	[44-46]
lncRNA NR-026689(up)	Diagnostic	NSCLC patients vs. healthy controls	Whole blood	[51]

Table 2. lncRNAs as biomarkers in lung cancer' serum

lncRNA	Function	Function	Sample	References
loc146880 and lc3b	Prognostic	tumor tissues and serum of lung cancer patients	serum	[52]
lncRNA XIST(up)	Diagnostic	NSCLC patients vs. healthy controls	Serum	[53]
lncRNA HIF1A-AS1(up)	Diagnostic	NSCLC patients vs. healthy controls	Serum	[53]
SOX2OT and ANRIL	Diagnostic and Prognostic	NSCLC patients vs. healthy controls	Serum	[54]

Table 3. lncRNAs as biomarkers in lung cancer' plasma

lncRNA	Function	Function	Sample	References
lncRNA 16(up)	Diagnostic	NSCLC patients vs. healthy controls	Plasma	[55]
lncRNA GAS5(up)	Diagnostic	NSCLC patients vs. healthy controls	Plasma	[56]
lncRNA-UCA1(up)	Diagnostic	NSCLC patients vs. healthy controls	Plasma	[57]
SPRY4-IT1(up)	Diagnostic and Prognostic	NSCLC patients vs. healthy controls	Plasma	[58]
ANRIL(up)	Diagnostic and Prognostic	NSCLC patients vs. healthy controls	Plasma	[58]
NEAT1 (up)	Diagnostic and Prognostic	NSCLC patients vs. healthy controls	Plasma	[58]
RP11-397D12.4(up)	Prognostic	NSCLC patients vs. healthy controls	Plasma	[59]
AC007403.1(up)	Prognostic	NSCLC patients vs. healthy controls	Plasma	[59]
ERICH1-AS1(up)	Prognostic	NSCLC patients vs. healthy controls	Plasma	[59]

microRNAs(eg:miR-21, miR-143,miR-155, miR-210, miR-372) [61-67] and two snoRNAs (snoRDs-66 and 78) have been reported as potential biomarkers for NSCLC [68].

LncRNAs radiochemotherapy in NSCLC

LncRNA in lung cancer chemotherapy-resistant

Current treatments against lung cancer are surgical treatment, and chemotherapy in combination with radiotherapy. DNA-damage repair(DDR) mechanisms are very important to maintain genomic stability. Platinum can cause DNA damage, particularly in cancer cells.

Platinum is used widely in chemotherapeutics of NSCLC [69, 70]. Platinum-based chemotherapy and targeted therapies are milestones in lung cancer treatment [71, 72]. Platinum arrests DNA replication during cell division [73]. LncRNAs are known to be involved in tumor development and metastasis, as well as chemotherapy resistance [74-76]. The expression of H19 in cisplatin-resistant A549/DDP cells was upregulated. Knockdown of H19 restored the response of A549/DDP cells to cisplatin [77]. And lncRNA CASC8 rs10505477 could serve as a possible risk factor for diagnosing lung cancer and the response to platinum-based treatment in lung cancer patients [78]. HOTAIR expression was significantly increased in cisplatin-resistant A549/DDP cells, and that siRNA-mediated silencing of HOTAIR could partly restore the responses of A549/DDP cells to cisplatin [79]. MEG3 expression is decreased in A549/DDP cells, and exogenic overexpression of MEG3 partially reversed the cisplatin resistance of A549/DDP cells through the upregulation of p53 and Bcl-xl expression [80]. Moreover, Yang et al. identified eight lncRNAs that were expressed differentially between A549 and A549/DDP cells [81]. Downregulation of lincAK126698 represses apoptosis induced by cisplatin in A549 cells through decreased naked cuticle homolog 2 expression and increased β -catenin expression that results in altered Wnt signaling [81]. Fang et al. reported that HOTAIR silencing reduced methylation of HOXA1 and enhanced the sensitivity of cancer cells to anticancer drugs in SCLC [82]. Ren reported that silencing the expression of KCNQ10T1 significantly inhibited chemoresistance to paclitaxel in LAD drug-resistant cells [83]. Ma et al. demonstrated that lncRNA TRPM2-AS enhanced the resistance of A549 cells to cisplatin [84]. Shi et al. reported that lncRNA ROR (regulator of reprogramming) silencing has the ability to enhance the sensitivity of lung adenocarcinoma cells to DDP by targeting PI3K/Akt/mTOR signaling pathway [85] that plays a key role in cell apoptosis and metastasis [86]. HOTTIP is reported to play a key role for in SCLC progression and chemoresistance by sponging miR-216a and promote BCL-2 expression, suggest it as a new prognostic biomarker for clinical management of SCLC [87].

LncRNA in lung cancer radiotherapy-resistant

Radiotherapy is essential for most lung cancer patients, especially for those with advanced stage NSCLC. In these patients, radiotherapy is especially critical [88, 89]. Radioactive rays could lead to physical, chemical and biological damages to both tumor cells and normal cells [90]. Recent reports show that lncRNAs are involved in the DNA damage response after radioactive rays, which may regulate the response to radiotherapy [91]. Cheng et al. demonstrated an inverse correlation between BANCER (BRAF activated non-coding RNAs) and radioresistance in mouse lung cancer tissues, when the mice were grafted with Lewis Lung cancer cells [92]. However, the detailed mechanisms about lncRNA and resistance to radiotherapy remain to be characterized.

LncRNAs in lung cancer EGFR resistance

EGFR-TKIs (EGFR tyrosine kinase inhibitors) and Programmed cell death protein 1 inhibitors are well known target therapies for NSCLC. Epidermal growth factor receptor (EGFR) super-family are regarded as a therapeutic target to NSCLC. It was firstly reported in 2004, patients who carry the EGFR mutations are sensitive to gefitinib [93]. And the never smokers with adenocarcinomas acquire EGFR gene mutation more frequently than

smokers, which causes them to be more sensitive to gefitinib or erlotinib [94]. However, acquired resistances are inevitable [95]. Kim H further found that the microRNA expression profile in the ALK rearrangement group were different from those in the EGFR and KRAS groups through clustering and discriminant analyses [96]. With the help of lncRNA microarray and bioinformatics analysis, Cheng showed the different lncRNA expression in

EGFR-TKIs-sensitive and -resistant human lung cancer cells, and speculated this disparate expression profile can play a pivotal role in resistance to EGFR-TKIs [97]. Cheng N and his colleagues first identified that 22, 587 lncRNAs were differentially expressed between gefitinib-sensitive and gefitinib-resistant lung cancer cells [97]. Bioinformatics analysis suggests that these differentially expressed lncRNAs regulate resistance to EGFR-TKIs by regulating their neighboring genes. Previous studies reported that the mechanism of EGFR-TKIs resistance is associated with cell proliferation and cell apoptosis [98-100]. In addition, Wu demonstrated that 1476 lncRNAs were dysregulated in EGFR-TKI-resistant cell line of lung adenocarcinoma, which further illustrated that lncRNAs serve as potential biomarkers in EGFR-TKI therapy-resistance [101]. Wang B found MIR31HG lncRNA expression increased gefitinib resistance in NSCLC cell lines through the EGFR/PI3K/AKT signaling pathway [102]. CASC9 expression was upregulated in PC9G (pc-9 gefitinib resistance) and knockdown of its expression increased the sensitivity of PC9G cells to gefitinib, while EWAST1 (Linc00227) is downregulated in PC9G cells and overexpressed EWAST1 also leads to increased sensitivity of PC9G cells to gefitinib [103]. lncRNA BC087858 can promote cells invasion and induce non-T790M mutation acquired resistance to EGFR-TKIs by activating PI3K/AKT and MEK/ERK pathways and EMT via up-regulating ZEB1 and Snail in NSCLC [104]. Dong demonstrated that GAS5 can reduce tumor growth under treatment with gefitinib and IGF-1R is a key downstream mediator of GAS5 [105]. Chao L et al. also reported that silencing the expression of GAS5 reduces the chemo-sensitivity of NSCLC cell to DDP through regulating miR-21/PTEN axis [106]. Linc00635-001 silencing accompanied by gefitinib treatment suppressed Akt activation and sensitized HCC827-8-1 cells to gefitinib-induced cytotoxicity [107]. Cheng N also found that lncRNA-BC200 mediates resistance to gefitinib [97]. Lin A et al. found LINK-A interacts with PtdIns(3, 4, 5)P3 to activate AKT and confer resistance to AKT inhibitors. Future studies are required to fully elucidate the mechanisms despite an emerging association between lncRNAs and drug resistance [108]. We summarize these lncRNAs in Table 4.

Table 4. lncRNAs in drug resistance

lncRNA	Function	Sample	References
H19(up)	cisplatin resistance	A549/DDP cells	[77]
lncRNA CASC8 rs10505477 (up)	cisplatin resistance	Lung cancer patients	[78]
HOTAIR(up)	cisplatin resistance	A549/DDP cells	[79]
HOTAIR(up)	anticancer drugs resistance	SCLC cells	[82]
MEG3(down)	cisplatin resistance	A549/DDP cells	[80]
lincAK126698(down)	cisplatin resistance	A549/DDP cells	[81]
lncRNA TRPM2-AS(up)	cisplatin resistance	A549/DDP cells	[84]
KCNQ1OT1(up)	Paclitaxel resistance	A549/Paclitaxel cells	[83]
lncRNA ROR	Increases DDP sensitivity	Lung adenocarcinoma cells	[85]
HOTTIP(up)	cisplatin and etoposide resistance	SCLC chemosensitive tissues compared with non-cancerous lung tissues/H69AR, H446AR cells	[87]
MIR31HG(up)	increases gefitinib resistance	NSCLC cell lines	[102]
CASC9(up)	increases gefitinib resistance	PC9G	[102]
EWAST1(Linc00227)(down)	increases gefitinib resistance	PC9G	[103]
lncRNA BC087858(up)	induce non-T790M mutation	NSCLC cell lines	[104]
GAS5 (up)	acquired resistance to EGFR-TKIs	in vitro and in vivo	[105]
linc00635-001(down)	increases gefitinib sensitivity	HCC827-8-1 cells	[107]
lncRNA-BC200(up)	increases gefitinib resistance	NSCLC cell lines	[97]

Conclusion

In conclusion, expression of numerous lncRNAs are dysregulated in lung cancer. Many of them are potential biomarkers of diagnosis and prognosis, especially drug resistance. It is suggested that lncRNAs can exert their functions through interactions with coding transcripts and proteins. However, the exact mechanisms of lncRNAs demand further studies to determine whether the differentially expressed lncRNAs regulate drug resistance in NSCLC and the lncRNAs are targets to overcome acquired drug resistance.

Acknowledgements

We are grateful for all the contributions that supported this study. This work was supported by National Natural Science Foundation of China Grants (Nos. 81702278, 81572281, 81401901, 81372515 and 81200366)

Disclosure Statement

The authors declare to have no competing interests.

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