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REVIEW ARTICLE

Long noncoding RNAs in lung cancer: what we know in 2015

Y. J. Xu[1] · Y. Du[2] · Y. Fan[1]

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Abstract Lung cancer ranks as the first most common cancer and the first leading cause of cancer-related death in China and worldwide. Due to the difficulty in early diagnosis and the onset of cancer metastasis, the 5-year survival rate of lung cancer remains extremely low. Long noncoding RNAs (lncRNAs), which lacking protein-coding ability, have recently emerged as pivotal participants in biological processes, often dysregulated in a range of cancers, including lung cancer. In this review, we highlight the recent findings of lncRNAs in lung cancer pathogenesis. While our understanding of lncRNAs in the onset and progression of lung cancer is still in its infancy, there is no doubt that understanding the activities of lncRNAs will certainly secure strong biomarkers and improve treatment options for lung cancer patients.

Keywords Lung cancer · lncRNA · NSCLC

Introduction

Lung cancer ranks as the first most common cancer and the first leading cause of cancer-related death in China and worldwide [1]. The NSCLC (non-small cell lung cancer) is the most prominent subgroup accounting for approximately 80 % of all lung cancer cases, which include adenocarcinomas, squamous cell carcinomas and large cell carcinomas [2]. While extensive efforts have been carried out in both research and clinical management, and despite the advances in the strategies of lung cancer diagnosis and treatment recent years, such as EGFR (epidermal growth factor receptor) and ALK (anaplastic lymphoma receptor tyrosine kinase) gene detection and targeted therapy, the prognosis remains very poor, with a 5-year overall survival rate of about 11 % [3]. This is mainly due to difficulty in early diagnosis and the incidence of cancer metastasis. The underlying molecular mechanism of lung cancer is quite complex and still has not been elucidated. Many gene mutations have been found to be associated with lung carcinogenesis, but they cannot explain all the clinical samples. Therefore, identifying new diagnostic and prognostic biomarkers, along with therapeutic targets, is still of paramount importance for lung cancer research.

Traditionally, most studies investigating carcinoma mechanisms focused on protein-coding genes. But with the development of new biological technologies such as deep sequencing, scientists are able to investigate gene expression in transcribed but not translated genes [4], such as noncoding RNAs (ncRNA) without the protein-coding ability [5]. MicroRNAs (miRNAs) are a subgroup of ncRNAs (19–24 nucleotides) that regulate targets at a posttranscriptional level, leading to either the inhibition of mRNA translation or the destruction of mRNA [6]. In addition to miRNAs, long ncRNAs (lncRNAs) are the other subtype of ncRNAs; otherwise, compared to miRNAs, the study of lncRNAs is in its infancy. According to the locations and characteristics of lncRNA, it can be divided into five categories (Fig. 1): (1) sense, (2) antisense, (3) bidirectional, (4) intronic, or (5) intergenic. Accumulating studies show that lncRNAs may regulate gene expression by diverse mechanisms, such as gene

✉ Y. Fan
21972483@qq.com; fanyun@zjcc.org.cn

[1] Department of Chemotherapy, Zhejiang Cancer Hospital, 310022 Hangzhou, China

[2] Department of Endocrinology, Sir Run Run Show Hospital, School of Medicine, Zhejiang University, 310016 Hangzhou, China

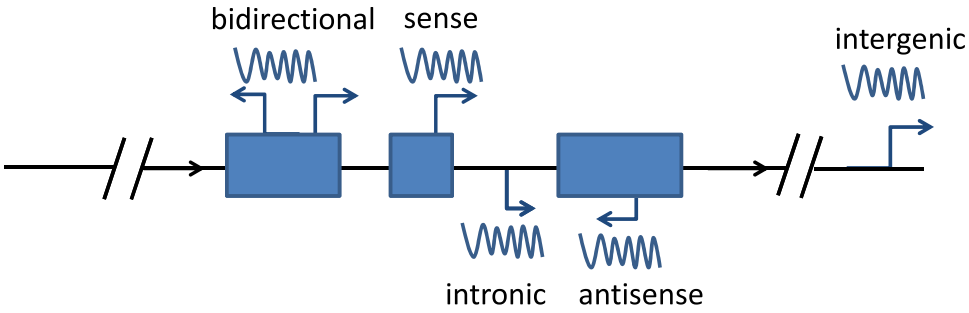

Fig. 1 The locations and characteristics of lncRNA

activation and suppression, chromatin modification and remodeling, mRNA splicing and translation, miRNA generation and sponges (Fig. 2).

Long noncoding RNAs

LncRNA are a class of noncoding RNA molecules at a cutoff point of 200 nucleotides in length to distinguish them from other ncRNAs, such as miRNAs [7]. It has been reported that over 30,000 lncRNAs can be detected across the human genome [8]. LncRNAs can be further divided into sense-antisense, bidirectional, intronic and intergenic lncRNAs, based on their expression location within a gene [9, 10]. And lncRNAs could regulate their targets at several levels, such as the transcriptional, posttranscriptional and translational levels [11]. LncRNAs can bind to the complementary sequences of their target genes, resulting in their target inhibition or activity reduction. LncRNAs can also recruit histone modification proteins or competitively bind to essential proteins initiating conformational change that can modulate the expression of their targets. There is also an intrinsic crosstalk existing between lncRNAs and miRNAs in cancer progression [12].

Although lncRNAs were discovered in early 1990, investigations of their expression and function have only emerged recently [13, 14]. Scientists have revealed a large number of biological functions of lncRNAs, for incidence, X chromosome inactivation, genomic imprinting, gene regulation, cell cycle regulation, protein scaffolding and chromatin modification. Heavy evidence has indicated that lncRNAs dysregulation is associated with human diseases, including cancer [15, 16]. Their aberrant expression in cancers has important pathogenetic consequences such as initiating metastasis development [17]. To date, a number of lncRNAs have been studied to be implicated in cancer progression, for example, BCAR4 in breast cancer [18], PCA3 in prostate cancer [19], and HULC in hepatocellular carcinoma [20]. In this context, the importance of lncRNAs of lung cancer will be discussed. The well-studied lung cancer-associated lncRNAs are summarized in Table 1.

LncRNAs and lung cancer

Highly up-regulated lncRNAs in lung cancer

Sox2 overlapping transcript (Sox2ot)

The lncRNA Sox2 overlapping transcript (Sox2ot) is localized on human chromosome 3q26.33. The amplification chromosome 3q26 is frequently detected in squamous cell carcinomas (SCC) from various localizations, including lung [21, 22]. Sox2ot is found up-regulated over

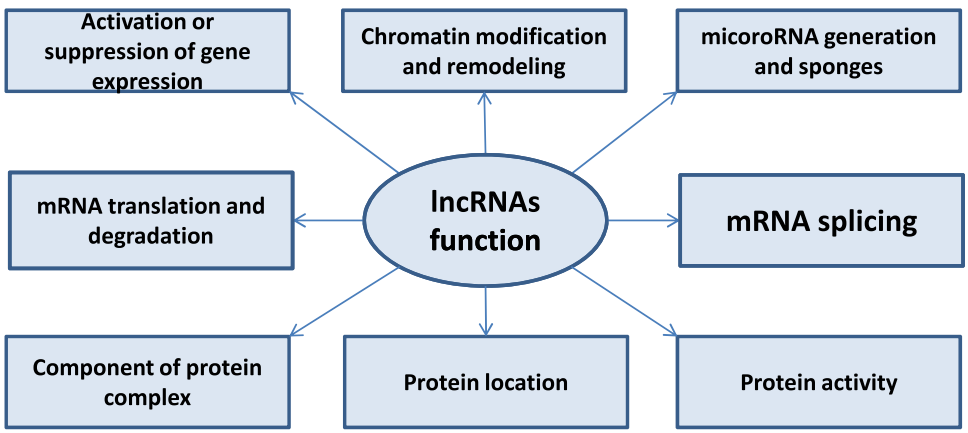

Fig. 2 The potential mechanisms of lncRNAs in regulating gene expression

Table 1 Well-studied lung cancer-associated lncRNAs

lncRNA	Expression	Chromosome	Pathway	Clinical association	Cell processes
Sox2ot	Up-regulated	3q26.33	EZH2	Poor survival	Proliferation
MALAT1	Up-regulated	11q13.1	Metastasis-associated	Poor prognosis	Proliferation, migration, metastasis, EMT, cell cycle
HOTAIR	Up-regulated	12q13.13	p21	Short disease-free survival and a poor prognosis	Motility, proliferation, migration, invasion
SCAL1	Up-regulated	5q14.3	NRF2	Cigarette smoking	Unknown
GAS6-AS1	Down-regulated	13q34	GAS6	Greater tumor size, lymph node metastasis and advanced TNM stage	Unknown
PANDAR	Down-regulated	6p21.2	p53, Bcl-2, NF-YA	Greater tumor size, lymph node metastasis and advanced TNM stage	Proliferation, apoptosis
SPRY4-IT1	Down-regulated	5q31.3	EZH2	Poor prognosis, tumor size, advanced pathological stage and lymph node metastasis	Apoptosis, proliferation, migration, invasion, metastasis, EMT

A summary of the well-studied lung cancer-associated lncRNAs. See text for other up-regulated lncRNAs in NSCLC

Sox2ot Sox2 overlapping transcript, *MALAT1* metastasis-associated lung adenocarcinoma transcript 1, *HOTAIR* Hox transcript antisense intergenic RNA, *SCAL1* Smoke and cancer-associated lncRNA–1, *GAS6-AS1* GAS6 antisense RNA 1, *PANDAR* promoter of CDKN1A antisense DNA damage activated RNA, *SPRY4-IT1* SPRY4 intronic transcript 1, *EZH2* enhancer of zeste 2 polycomb repressive complex 2 subunit, *NRF2* Nf-E2 related factor 2, *NF-YA* nuclear factor Y-box A, *EMT* epithelial–mesenchymal transition

twofold in 53.01 % of human primary lung cancers (44/83). Interestingly, the expression level of Sox2ot is significantly higher in SCCs than that in adenocarcinomas (ADCs), suggesting that Sox2ot may be a useful marker to distinguish SCCs from ADCs of the lung cancer. Data also showed that high Sox2ot expression predicted poor survival in patients with lung cancer ($P < 0.01$), implying that Sox2ot might be a novel prognostic factor for lung cancer. Further study showed that knocking down Sox2ot inhibited lung cancer cell proliferation by inducing G2/M arrest and reducing both the mRNA and protein level of EZH2. Consistently, previous studies showed that EZH2 is associated with the malignancies of NSCLC and is a negative prognostic indicator for NSCLC [23, 24]. Their data suggested that Sox2ot plays an important role in regulating lung cancer cell proliferation, and may represent a novel prognostic indicator for lung cancer, especially for the SCCs [25].

Metastasis-associated lung adenocarcinoma transcript 1(MALAT1)

MALAT1 (metastasis-associated lung adenocarcinoma transcript 1), which is also referred to as NEAT2 (nuclear-enriched abundant transcript 2), is one of the first discovered cancer-associated lncRNAs and highly conserved amongst mammals [26]. There are two alternative proposed mechanisms of action for MALAT1: (1) MALAT1 may regulate alternative splicing of pre-mRNAs by modulating serine/arginine splicing factor phosphorylation [27]; (2) MALAT1 might interact with the demethylated CBX4 (chromobox homolog 4), also known as Pc2 (polycomb 2), controlling the relocalization of growth control genes between polycomb bodies and interchromatin granules [28]. But the exact function of MALAT1 is still unelucidated.

In NSCLC, MALAT1 was firstly identified as a prognostic marker for metastasis and survival specifically in the early stages of lung ADCs [29]. In lung SCCs, MALAT1 expression is also up-regulated and associated with poor prognosis, tumor growth and cell migration [30, 31]. Besides, Tony et al. reported that MALAT1-deficient lung cancer cells are impaired in migration and form smaller and fewer tumor nodules than the wild-type counterparts in a mouse xenograft model. They uncover the function of MALAT1 in lung cancer metastasis through regulating metastasis-associated genes. Moreover, targeting MALAT1 expression reduces the formation of lung cancer metastasis in vivo and indicates MALAT1 as a potential therapeutic target in lung cancer [32]. Consistently, the level of MALAT1 was found significantly higher in brain metastasis samples than non-brain metastasis samples and was also increased in highly invasive subline of brain metastasis lung cancer cells H1915. They also found that silencing MALAT1 inhibits H1915 cells migration and metastasis by inducing epithelial–mesenchymal transition (EMT) [33]. In view of these findings, MALAT1 is likely to represent an important functional and prognostic factor and a potential therapeutic target for lung cancer.

Hox transcript antisense intergenic RNA (HOTAIR)

The lncRNA HOTAIR (Hox transcript antisense intergenic RNA) is one of the few biologically well-studied lncRNA that is associated with human HOX loci and cancer metastasis, and has been identified as an oncogenic lncRNA that is involved in the progression of a variety of cancers as a negative prognostic biomarker [34–36]. For incidence, it is up-regulated in breast cancer and is associated with metastasis formation and a poor prognosis [36]. Yet, little is known about the effect of HOTAIR in either NSCLC or small cell lung cancer (SCLC). In NSCLC, HOTAIR was found highly expressed in lymph node metastasis samples when compared to the matched primary lung cancer tissues. Further functional studies showed that it is also involved in lung cancer cells motility, proliferation, migration and invasion, indicating a short disease-free survival and a poor prognosis [37–39]. Moreover, HOTAIR was found to be associated with cisplatin resistance in lung adenocarcinoma cells through downregulating the expression of p21 [40]. SCLC is another subtype of lung cancer with poor prognosis. HOTAIR was also found dysregulated in SCLC. The highly expressed level of HOTAIR in SCLC was related to more lymphatic invasion and more relapse than the low-expression subgroup. Moreover, knockdown of HOTAIR in SCLC cells inhibited the proliferation activity and invasiveness of cancer cells by targeting gene expression, such as the up-regulation of cell adhesion-related genes, and mucin production-related genes [41]. These results suggest that HOTAIR may function as an oncogene both in NSCLC and SCLC.

Smoke and cancer-associated lncRNA–1 (SCAL1)

Cigarette smoking-induced toxicity is the main cause of lung cancer incidence. But the underlying molecular mechanisms of gene regulation induced by cigarette smoking that leads to lung cancer occurred remain unclear. There is a report describing a new identified lncRNA-smoke and cancer-associated lncRNA–1 (SCAL1), which is located in chromosome five and is regulated by nuclear factor erythroid two-related factor (NRF2) transcriptionally. The up-regulation of SCAL1 is elevated in numerous lung cancer cell lines, such as A549, CL1–0, CL1–5, H1975, HCC-827, NCI-H292, and PC9. Moreover, it also functions in mediating protection against cigarette smoking-induced toxicity [42]. Thus, it will be interesting to further study the mechanisms and clinical use of SCAL1 for lung cancer.

Other novel up-regulated lncRNAs

In recent few months, microarray analysis was widely used to study the expression patterns of lncRNAs in NSCLC tissues. Most studies are further focusing on the up-regulated lncRNAs in NSCLC, such as LINC01133 (only up-regulated in lung squamous cell cancer), RGMB-AS1, DLX6-AS1, Lnc_bc060912, NEAT1, HNF1A-AS1, ANRIL, BCYRN1 and AK001796 [43–51]. Most of the highly expressed lncRNAs in NSCLC tissues were associated with higher TNM stage, advanced lymph node metastasis and poorer overall survival. The major limitation of the above studies is that there are no more functional studies of the dysregulated lncRNAs.

Down-regulated lncRNAs in lung cancer

LncRNAs are either up-regulated or down-regulated in carcinogenesis. For incidence, GAS6-AS1, PANDAR, SPRY4-IT1, LET and MEG3 were reported to be decreased in lung cancer [52–56]. Both GAS6-AS1 and PANDAR were found generally down-regulated in NSCLC tissues when compared with those pair-matched adjacent normal tissues. And decreased GAS6-AS1 and PANDAR expression was negatively correlated with some clinical characteristics of lung cancer, such as greater tumor size, lymph node metastasis and advanced TNM stage. Moreover, GAS6-AS1 and PANDAR could serve as an independent predictor of overall survival in NSCLC [52, 53]. Further study indicated that PANDAR was a direct transcriptional target of p53 in NSCLC cells and overexpression of PANDAR could inhibit the proliferation of NSCLC cells. They also showed that PANDAR-mediated cell proliferation inhibition is in part associated with the transcriptional modulation of Bcl-2 by interacting with NF-YA, thus affecting NSCLC cell apoptosis. In a word, it is worth to further study the p53/PANDAR/NF-YA/Bcl-2 interaction pathway, which might serve as targets for NSCLC diagnosis and therapy in the future [52].

SPRY4-IT1 was reported as an EZH2-mediated lncRNA, which was down-regulated and correlated with a poor prognosis of NSCLC as its expression level was significantly correlated with tumor size, advanced pathological stage and lymph node metastasis [54]. Functional study showed that SPRY4-IT1 could induce NSCLC cell apoptosis, promote NSCLC cell proliferation, migration, invasion and metastasis by affecting the epithelial–mesenchymal transition (EMT) [54]. Hence, the down-regulation of lncRNAs in lung cancer may be negative prognostic factors for lung cancer patients, indicative of poor survival rates, and higher risks for cancer metastasis.

Biomarker lncRNAs

As far as the low overall 5-year survival rate of lung cancer is concerned, it is obvious that finding early stage lung cancer may reduce the mortality. In fact, searching for highly sensitive biomarkers for the diagnosis of early stage lung cancer is one of the most major research efforts in the lung cancer field. Besides, a better understanding of the genetic and molecular aberrations of lung cancer is likely to be the crux of early diagnosis [57, 58]. Very recently, a panel of 5-lncRNA was determined to distinguish early stage lung adenocarcinoma from non-tumorous tissues samples with high sensitivity (96.8 %) and specificity (92.1 %), which was significantly higher than those obtained by any single lncRNA alone [58].

Based on the above studies, lncRNAs are identified as potential biomarkers for NSCLC diagnosis, metastasis and prognosis. Biomarkers need to be easily detectable in body fluids with high specificity and sufficient sensitivity. Hence, Weber et al. detected the expression level of MALAT1 in the cellular fraction of peripheral human blood in NSCLC patients. Results indicated that MALAT1 was detectable in peripheral blood and showed different expression of MALAT1 between cancer patients and non-cancer controls. But the sensitivity is too low (56 %) for the use of MALAT1 as a single biomarker for NSCLC [59]. Without doubt, the impact of lncRNAs in lung cancer diagnosis, metastasis and prognosis as biomarkers is potentially important and enormous, while much more research is needed to reassure the importance.

Conclusion

As far as we know, lncRNAs are abundant and diverse, the expression and function of majority lncRNAs remain unclear in lung cancer. Hence, the identification of new lung cancer-associated lncRNAs will continue consistently at a rapid pace, and much more research is needed. Without doubt, there are also some unraveling but previously found and yet to be published lncRNAs which will have impact on the clinical management of lung cancer patients. Difficulties in early diagnosis and the metastasis are major points that the mortality rate remains high in lung cancer. Recent data suggest that lncRNAs may be novel candidate biomarkers for both the early detection and the prognosis of lung cancer gives clinical hope for lung cancer patients potentially undergoing lncRNA-based diagnosis and therapy in combination with traditional methods. Besides, other ncRNAs have also proved to play important roles in cancer pathogenesis, such as miRNAs, snoRNA, siRNAs and piRNAs. And there exist important intrinsic linkages between ncRNAs. Therefore, it will be interesting to combine the lncRNAs with other ncRNAs in the research in the onset and progression of lung cancer in the future.

In the last decade, there are significant progressions in understanding the underlying molecular pathology and significant heterogeneity of lung cancer, especially the NSCLC. Multiple signaling pathways, including ncRNAs, protein-coding genes and driver mutations, have been identified as oncogenes or suppressor genes that are associated with malignant transformations. In fact, in the clinical practice, the vast majority of the lung cancer patients have no known driver mutations detected, and they are still treated with standard cytotoxic chemotherapy. Moreover, acquired resistance is common in patients with a known driver mutation. Thus, we are still challenged with the goal to elucidate the underlying molecular mechanism of lung cancer development and progression, to find new molecular biomarkers for lung cancer diagnosis and prognosis and to deliver unique personalized medicine. As the above strong evidences that the up-regulation and down-regulation of many lncRNAs are associated with lung cancer, targeting these lncRNAs in combination with other molecular targets could have a potential value for lung cancer research and therapy.

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