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Review:

Role of LINC00152 in non-small cell lung cancer*

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Abstract: Non-small cell lung cancer (NSCLC) accounts for about 85% of all lung cancer cases. The pathogenesis of NSCLC involves complex gene networks that include different types of non-coding RNAs, such as long non-coding RNAs (lncRNAs). The role of lncRNAs in NSCLC is gaining an increasing interest as their function is being explored in various human cancers. Recently, a new oncogenic lncRNA, LINC00152 (cytoskeleton regulator RNA (CYTOR)), has been identified in different tumor types. In NSCLC, the high expression of LINC00152 in tumor tissue and peripheral blood samples has been shown to be associated with worse prognoses of NSCLC patients. Overexpression of LINC00152 has been confirmed to promote the proliferation, invasion, and migration of NSCLC cells in vitro, as well as increase tumor growth in vivo. This review discusses the role of LINC00152 in NSCLC.

Key words: Long non-coding RNA; LINC00152; Non-small cell lung cancer; Proliferation; Prognosis
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1 Introduction

Lung cancer is one of the most common malignancies and is the leading cause of cancer-related mortality worldwide (Fidler and Bray, 2018). Around 85% of all lung cancer cases have been attributed to non-small cell lung cancer (NSCLC), which includes different histological types such as lung adenocarcinoma, squamous cell carcinoma, and large cell lung cancer. Among these subtypes, lung adenocarcinoma is the most common NSCLC (Ettinger et al., 2015). Despite the gratifying progress in the understanding of its molecular mechanisms and in the discovery of potential clinical treatments, the prognosis of lung cancer patients remains unsatisfactory. Indeed, most patients are diagnosed after reaching advanced stages, which hinders their chances to receive optimal treatment. Consequently, the five-year overall survival rate of NSCLC is only about 15% (Torre et al., 2016).

The role of long non-coding RNAs (lncRNAs) in the pathogenesis and progression of NSCLC is gaining increasing attention with the rapid development of high-throughput sequencing and various omics technologies (Esfandi et al., 2019). Some lncRNAs, such as HOX transcript antisense RNA (HOTAIR) (Liu et al., 2013), maternally expressed 3 (MEG3) (Liu et al., 2015), and colon cancer-associated transcript 1 (CCAT1) (Chen J et al., 2016), have been shown to participate in the etiology and deterioration of NSCLC, which can affect NSCLC diagnosis and treatment. Therefore, illuminating the function of lncRNAs would provide new insights to explore the molecular characteristics of NSCLC and would offer new possibilities to develop more effective therapeutic strategies (Bhan et al., 2017).

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A newly discovered lncRNA, LINC00152 (cytoskeleton regulator RNA (CYTOR)), has been recently shown to exert various carcinogenic effects in a variety of tumors and has been demonstrated to serve as a potential diagnostic and prognostic biomarker (Bian et al., 2017; Deng et al., 2017; Cai et al., 2018; Chen PX et al., 2018). This review focuses on the pivotal role of LINC00152 in NSCLC.

2 Characteristics of lncRNA

While having little or no protein-coding capacity, lncRNAs are usually more than 200 nucleotides in length and participate in multiple biological processes (Dey et al., 2014). During tumor progression, lncRNAs play vital regulatory roles at epigenetic, transcriptional, and post-transcriptional levels (Orom et al., 2010). The function of lncRNAs is highly associated with their localization within the cells. In the nucleus, lncRNAs regulate gene expression by binding to transcription factors, chromatin modifiers, and heterogeneous nuclear ribonucleoproteins (hnRNPs). They can also regulate splicing, stabilization, and translation of host messenger RNAs (mRNAs) through post-transcriptional mechanism (Orom et al., 2010). On the other hand, lncRNAs in cytoplasm cannot only regulate the stability and translation of mRNAs, but also are involved in cellular signaling cascades. They can also bind specific microRNAs (miRNAs) as competing endogenous RNA (ceRNA), thus acting as "miRNA sponges" to protect target mRNAs from inhibition (Fatica and Bozzoni, 2014). In addition, some lncRNAs in the cytoplasm that contain small open reading frame (ORF) can be translated into bioactive short peptides (Choi et al., 2019).

LncRNAs act in various cancers either as tumor suppressors or oncogenes (Wang Y et al., 2018). In some classical tumor-related signaling pathways such as p53, nuclear factor-κB (NF-κB), and phosphoinositide-3-kinase (PI3K)/AKT, lncRNAs can serve as the scaffold for receptors, protein kinases, and transcription factors in signaling cascades (Peng et al., 2017).

3 Relation of overexpression of LINC00152 with worse prognosis of NSCLC patients

The LINC00152 gene is located on chromosome 2p11.2, with a transcript length of 828 nucleotides. The localization of LINC00152 differs between tumor cells from different origins (Table 1). Nevertheless, LINC00152 acts as an oncogene regardless of its localization in tumor cells. Yu Y et al. (2017) reviewed the pivotal oncogenic effect of LINC00152 in different human cancers, including gastric cancer, hepatocellular carcinoma, colon cancer, gallbladder cancer, and renal cell carcinoma. While the carcinogenic function of LINC00152 has been confirmed in multiple cancers (Table 2), only one study on colon cancer showed contradictory findings about the expression and mechanism of action of LINC00152 (Zhang et al., 2016). This discrepancy could be related to different factors such as the sample size, demographic characteristics, polymerase chain reaction (PCR) primers, experimental protocols, and laboratory conditions.

LINC00152 is overexpressed in lung adenocarcinoma tissues and can be used as a predictor of reduced patient survival (Table 3). It serves as an independent risk factor for disease-free survival (DFS) and overall survival (OS) (Zhang PP et al., 2017).

Table 1 Predominant distribution of LINC00152 in tumor cells from different origins

Type of cancer	Nucleus	Cytoplasm	Reference
Hepatoma	Yes		Ji et al., 2015
Gastric cancer		Yes	Zhou et al., 2015; Chen WM et al., 2016
Osteosarcoma		Yes	Zheng et al., 2019
Ovarian cancer		Yes	Chen PX et al., 2018
Glioma		Yes	Reon et al., 2018
Breast cancer	Yes	Yes	Wu et al., 2018; Shen et al., 2019
Kidney cancer	Yes	Yes	Wang et al., 2017
Lung cancer	Yes	Yes	Chen et al., 2017; Feng et al., 2017; Zhang and Li, 2018
Colon cancer	Yes	Yes	Bian et al., 2017; Nishizawa et al., 2018; Wang X et al., 2018

Table 2 Expression of LINC00152 in tumor tissues from different origins

Type of cancer	Expression level	Reference
Hepatoma	↑	Ji et al., 2015; Ma et al., 2018
Gastric cancer	↑	Zhao et al., 2015; Zhou et al., 2015; Chen WM et al., 2016; Yang et al., 2016; Huang et al., 2018; Wang HF et al., 2019
Osteosarcoma	↑	Zheng et al., 2019
Ovarian cancer	↑	Chen PX et al., 2018
Glioma	↑	Yu MJ et al., 2017; Cai et al., 2018; Chen X et al., 2018; Liu et al., 2018; Reon et al., 2018; Zhu et al., 2018
Breast cancer	↑	Wu et al., 2018; Shen et al., 2019
Kidney cancer	↑	Wu et al., 2016; Wang et al., 2017
Gallbladder cancer	↑	Cai et al., 2016, 2017
Tongue squamous cell carcinoma	↑	Yu JJ et al., 2017
Oral cancer	↑	Li MH et al., 2018; Chen et al., 2019
Esophageal squamous cell carcinoma	↑	Hu HB et al., 2016; Liu DL et al., 2019
Hemangioma	↑	Wang YL et al., 2019
Acute myeloid leukemia	↑	Zhang and Tao, 2019
Multiple myeloma	↑	Yu et al., 2018
Retinoblastoma	↑	Li SH et al., 2018
Papillary thyroid cancer	↑	Sun et al., 2019
Lung cancer	↑	Chen et al., 2017; Feng et al., 2017; Li et al., 2017; Ma et al., 2017; Nötzold et al., 2017; Xu et al., 2017; Zhang PP et al., 2017; Reon et al., 2018; Zhang and Li, 2018; Zhao et al., 2018; Liu ZZ et al., 2019
Colon cancer	↑	Qiu and Yan, 2015; Bian et al., 2017; Nishizawa et al., 2018; Wang X et al., 2018; Yue et al., 2018
	↓	Zhang et al., 2016

Table 3 LINC00152 expression in NSCLC tissues

Tissue sample (*n*)	Expression level	Correlation	No correlation	Reference
101	↑	Poor prognosis	Age, gender, smoking history, tumor differentiation, tumor stage, lymph node status, KRAS mutation	Feng et al., 2017
60	↑	TNM stage, tumor size, lymph node metastasis, poor survival	Age, gender, smoking history	Chen et al., 2017
64	↑	Tumor size, advanced TNM stage, lymph node metastasis, shorter overall survival	Gender, age, smoking status, differentiation grade	Zhang and Li, 2018
110	↑	Lymph node metastasis, distant metastasis, TNM stage, decreased survival	T stage of lung adenocarcinoma	Zhang PP et al., 2017
27	↑			Nötzold et al., 2017
30	↑	EGFR expression		Zhang Y et al., 2017
80	↑	Smoking history, tumor size, differentiation, metastasis		Liu ZZ et al., 2019
90	↑		Age, gender, tumor stage, metastasis	Zhao et al., 2018
72		Tumor size, tumor stage	Age, gender, histology subtype, lymph node metastasis	Li et al., 2017

EGFR: epidermal growth factor receptor; TNM: tumor-node-metastasis

This conclusion has been also confirmed by other reports (Feng et al., 2017; Reon et al., 2018) on the Gene Expression Omnibus (GEO) (Seo et al., 2012) and The Cancer Genome Atlas (TCGA) databases (Collisson et al., 2014). Zhao et al. (2018) analyzed the expression profiles of lncRNAs in three pairs of lung adenocarcinoma tissues and adjacent normal tissues. They found that LINC00152, LINC00691, and LINC00578 are the most significantly up-regulated lncRNAs in lung adenocarcinoma tissues, compared with adjacent tissues. The results were further identified by quantitative real-time polymerase chain reaction (qRT-PCR) in 90 lung adenocarcinoma tissue samples. Unexpectedly, LINC00152 showed no significant correlation with the clinicopathologic characteristics including age, gender, tumor stage, or metastasis (Zhao et al., 2018). These inconsistent results indicate that future studies warrant more accurate experimental designs and standard operating procedures with larger sample sizes.

4 Circulating LINC00152 as a biomarker for NSCLC

Tumor cells can release a large number of RNAs into the peripheral blood (Rapisuwon et al., 2016). These RNAs, such as lncRNAs, can be used as biomarkers to quantitatively measure the progression of pathological disorders in tumor patients (Hu HB et al., 2016; Hu XD et al., 2016; Yang et al., 2016; Mao et al., 2019). Some lncRNAs, such as metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), HOTAIR, and growth arrest specific 5 (GAS5), have been found to be abnormally expressed in the serum of patients with NSCLC (Xie et al., 2018).

Li et al. (2017) measured the expression level of LINC00152 in the plasma of 100 NSCLC patients. They found that LINC00152 expression is markedly up-regulated and significantly associated with tumor size and stage. They also observed that LINC00152 was stable in whole blood and plasma samples by environmental intervention through the inappropriate storage condition of plasma samples. In addition, LINC00152 level was able to effectively discriminate NSCLC patients from healthy controls and patients with benign lung disease, although there was no apparent variance in plasma LINC00152 level between the latter two groups. Moreover, there was a positive relationship between plasma LINC00152 level and a traditional NSCLC marker, carcinoembryonic antigen (CEA). The combined measurement of LINC00152 and CEA showed a higher diagnostic ability, compared with LINC00152 or CEA alone. Even for NSCLC patients in stage I, the plasma level of LINC00152 showed higher diagnostic accuracy than that of CEA. Li et al. (2017) also observed a significant positive correlation between LINC00152 level in tumor tissue and that in plasma samples. Furthermore, post-operative plasma LINC00152 levels in 47 patients one month after surgery were lower than the preoperative levels in the same patients. In relapsed patients, plasma LINC00152 level rapidly rebounded, suggesting that circulating lncRNAs could be mainly originated from tumor cells.

Smoking is one of the causes of lung cancer. A recent report demonstrated that LINC00152 was present at higher levels in the serum of smokers and was positively correlated with the exposure dose (Liu ZZ et al., 2019). Li J et al. (2015) also reported that lncRNAs in circulating peripheral blood can be used as biomarkers of diagnosis and prognosis. One explanation of the potential mechanism is that lncRNAs can be selectively encapsulated into membrane-covered vesicles including exosomes, particles, and apoptotic bodies. LncRNAs can also be folded into complex secondary and tertiary structures, or can bind to proteins to avoid degradation. Another possible explanation is that circulating lncRNAs resist RNase digestion through methylation, adenylation, and uridinylation (Li QE et al., 2015).

5 Effect of LINC00152 on NSCLC cells

LINC00152 is highly expressed in lung cancer cells (Liu ZZ et al., 2019). Chen et al. (2017) examined LINC00152 level in six lung adenocarcinoma cell lines: A549, SPCA1, PC-9, H1299, H1975, and H226. They found that A549 and SPCA1 cells had the highest expression level of LINC00152, while H1299 cells expressed the lowest level. The heterogeneity of basal LINC00152 expression within cell lines of various options can be exploited to perform both knockdown and overexpression experiments to elucidate in vitro function (Chen et al., 2017).

Overexpression of LINC00152 in NSCLC cells facilitates cell proliferation, invasion, and migration. In contrast, down-regulation of LINC00152 significantly inhibits lung cancer cells' proliferation, invasion, and migration in vitro. It also restrains lung tumor growth and distant metastasis in vivo (Zhang PP et al., 2017; Zhang Y et al., 2017). Zhang Y et al. (2017) speculated that the oncogenic effect of LINC00152 depends on epidermal growth factor receptor (EGFR)/PI3K/AKT signaling pathway. However, their study lacked direct evidence. Interestingly, studies on gastric cancer and vascular endothelial cells confirmed that LINC00152 can activate PI3K/AKT signaling pathway through direct binding to EGFR (Zhou et al., 2015; Teng et al., 2017).

Epithelial mesenchymal transition (EMT) plays a critical role in the process of tumor metastasis. Ectopic expression of LINC00152 expedites EMT program. Some EMT markers (for example, epithelial marker *E*-cadherin) were negatively correlated with LINC00152 level. Other EMT markers, such as mesenchymal markers *N*-cadherin and vimentin, were positively correlated with LINC00152 level in various types of tumors (Zhang Y et al., 2017; Hu et al., 2018; Li MH et al., 2018).

LINC00152 regulates EMT process through several canonical molecular pathways. For example, LINC00152 was shown to mediate EMT process through Wnt/β-catenin signaling pathway in colon cancer (Yue et al., 2018). LINC00152 blocks casein kinase 1 (CK1)–β-catenin interaction by competitively binding non-phospho-β-catenin^{Ser45}. Then it drives β-catenin nuclear translocation. After entering nucleus, β-catenin binds to T-cell factor (TCF). The β-catenin/TCF complex then induces nuclear LINC00152 transcription and directly *trans*-activates downstream target genes via TCF-binding elements (TBEs) that are presented in their *cis*-regulatory regions, thus forming a positive feedback loop in colon cancer cells to promote EMT process. Another report in colon cancer cells found a direct interaction between LINC00152 and two RNA binding proteins, nucleolin (NCL) and Sam68 (Src-associated in mitosis, 68 kDa). The NCL-LINC00152-Sam68 complex was shown to promote colon cancer progression and EMT process by activating NF-κB signaling pathway. In this progress, EXON1 of LINC00152 is indispensable for its interaction with NCL and Sam68 (Wang X et al., 2018). These results suggest that the regulatory network by LINC00152 is complex and that future studies to analyze the mechanism of LINC00152 in EMT process of lung cancer cells will require referral to the current evidence.

Through analyzing RNA-Seq data, Feng et al. (2017) confirmed that LINC00152, with histone acetylation, was highly expressed in 30 NSCLC cell lines. However, the DNA copy number or promoter DNA methylation of LINC00152 genomic locus was not changed. After silencing LINC00152 in 12 lung cancer cell lines, the authors observed that cell proliferation was repressed in nine cell lines. Interestingly, while the growth of PC-9 (EGFR mutant) and H838 (EGFR wild type) cells was both most sensitive to LINC00152 knockdown, the invasion abilities of these two cell lines were not affected. In addition, in contrast to the results of Zhang PP et al. (2017), LINC00152 knockdown did not change the growth of H1650 lung cancer cells. Hence, the underlying reason behind these findings warrants further investigation.

The p38 mitogen-activated protein kinase (MAPK) pathway is known to respond to various extracellular stresses (Cuadrado and Nebreda, 2010). Cyclic adenosine monophosphate (cAMP)-responsive element binding protein 1 (CREB1), signal transducer and activator of transcription 1 (STAT1), and signal transducer and activator of transcription 3 (STAT3) are all key elements in this signaling pathway. CREB1 modulates cell cycle and apoptosis by up-regulating the expression of cyclin E1 (CCNE1). P38 knockdown can lead to increased expression of phosphorylated STAT3 (p-STAT3), which in turn up-regulates other genes involved in tumor cell proliferation and survival, such as MYC proto-oncogene (c-MYC), cyclin D1 (CCND1), cyclin D2, B-cell lymphoma-extra large (BCL-XL), and myeloid cell leukemia 1 (MCL1). Feng et al. (2017) showed that small interfering RNA (siRNA)-based knockdown of LINC00152 reduced the protein expression of p38a, STAT1, STAT3, CREB1, CCNE1, and c-MYC. However, the mRNA expression of the genes did not change, except for STAT3 and CCNE1, which suggests that LINC00152 might regulate STAT3 and CCNE1 expression at transcriptional level, while it can regulate the expression of the other genes at post-transcriptional level. It is worth noticing that the protein expression of EGFR, AKT serine/threonine kinase 1 (AKT1), or

extracellular signal-regulated kinase 1/2 (ERK1/2) did not change in this study, which suggests that cell growth would be affected if LINC00152 reaches a certain level and that the genomic background might be a key element for LINC00152 to exert its effects on cell growth. These results are very encouraging to further conduct follow-up studies on the activity of LINC00152 in NSCLC.

6 LINC00152 involved in cell cycle arrest and apoptosis in lung adenocarcinoma

Zhang Y et al. (2017) reported that LINC00152 knockdown impaired cell proliferation, invasion, and metastasis in lung adenocarcinoma. LINC00152 knockdown also promoted cell apoptosis and induced cell cycle arrest in G_1 phase. Their results showed that the protein expression levels of EGFR, PI3K, AKT, fibronectin, and vimentin in tumor cells significantly decreased after LINC00152 down-regulation. In contrast, the protein level of cyclin-dependent kinase inhibitor 1A (p21), associated with cell cycle arrest and apoptosis (El-Deiry, 2016), was obviously increased (Zhang Y et al., 2017). The enhancer of zeste homolog 2 (EZH2) is a core catalytic element of polycomb repressive complex 2 (PRC2), which inhibits the transcription of target gene and affects cancer progression by modulating histone H3 lysine 27 trimethylation (H3K27me3). A study on gastric cancer demonstrated that LINC00152 can inhibit target gene expression at epigenetic level by recruiting EZH2 to cyclin-dependent kinase inhibitor 2B (p15) and p21 promoters through H3K27me3, thereby promoting cell proliferation and cell cycle progression (Chen WM et al., 2016).

Chen et al. (2017) demonstrated that LINC00152 knockdown can promote apoptosis and induce cell cycle at G_1 phase. In contrary to the results reported by Feng et al. (2017), they observed that LINC00152 was predominantly distributed in the nucleus of A549 and SPCA1 cells, and it can directly bind to EZH2 and lysine demethylase 1A (LSD1) in lung cancer cells. Their result of chromatin immunoprecipitation (ChIP) further demonstrated that EZH2, but not LSD1, was bound to the promoter locus of interleukin 24 (IL-24). Correspondingly, LINC00152 knockdown reduced H3K27me3 occupation in IL24 promoter region. These results indicated that, at least partially, LINC00152 can repress IL24 expression at epigenetic level by recruiting EZH2 to IL24 promoter, thereby promoting the proliferation of lung adenocarcinoma cells. A study on renal cancer also showed that LINC00152 can inhibit cyclin-dependent kinase inhibitor 2A (p16) expression through interaction with EZH2 and LSD1 at epigenetic level by regulating H3K27me3 (Wang et al., 2017). These findings revealed that the mechanism of LINC00152 is heterogeneous, even in homologous tumors, which should be considered in future studies.

Liu ZZ et al. (2019) established a malignant transformed cell model (16HBE-M) by treating human bronchial epithelial cell lines with cigarette smoke extract (CSE). During this process, LINC00152 promoted cell malignant transformation by binding to miR-193b, leading to the up-regulated CCND1. Silencing LINC00152 inhibited proliferation, invasion, and metastasis of 16HBE-M and lung cancer cells along with cell cycle arrest at G_0/G_1 phase. In contrast, Reon et al. (2018) reported that the interaction with PRC2 or the M8 hairpin RNA is not necessary for LINC00152-mediated invasion. They also ruled out the "miRNA sponge" mechanism proposed by Zhang and Li (2018). M8 is a protein-binding site that constitutes nucleotides 280–401 of the stem-loop structure at the 3' end of LINC00152, and its overexpression has been shown to stimulate glioma cells invasion.

While LINC00152 and CCND1 were up-regulated with increased dose and duration, miR-193b level was down-regulated in 16HBE-M cells acutely exposed to CSE. Similarly, the expression of *E*-cadherin decreased, while that of *N*-cadherin and vimentin increased after CSE treatment. In addition, the proportion of cells in G_0/G_1 phase was remarkably reduced, while that in S and G_2/M phases was obviously elevated. LINC00152 or CCND1 knockdown lowered the mRNA and protein expression of cyclin-dependent kinase 4 (CDK4), CDK6, retinoblastoma protein (Rb), and E2F transcription factor 1 (E2F1), which indicates that LINC00152 can control cell cycle and proliferation through CCND1 and its downstream CDK4/CDK6/Rb/E2F1 pathway (Liu ZZ et al., 2019).

It has been shown that LINC00152 plays a crucial role in cell cycle progression through the regulation of mitosis. LINC00152 depletion induced mitotic arrest in about 75% HeLa cells, of which 42%

underwent apoptosis, 28% exited mitosis, and 5% experienced cytokinesis failure. The remaining 25% of cells died directly at an earlier time point (12–24 h). Therefore, apoptosis may not be a direct consequence of LINC00152 knockdown, and it might be a follow-up event that occurs after cell cycle arrest (Nötzold et al., 2017).

The mechanism of LINC00152 in NSCLC is still far from being elucidated. However, clues can be obtained from other diseases to identify potential targets of LINC00152 regulatory network. The cellular distribution and the expression level of LINC00152 followed by manual intervention should be taken into account in in vitro experiments. Until now, in vivo studies using lncRNA knockdown strategies to reduce NSCLC tumor growth are very limited (Gutschner et al., 2013). This could be mainly related to the challenging nature of the experimental strategies, such as RNA interference (RNAi), antisense oligonucleotide (ASO), morpholinos, and clustered regularly interspaced short palindromic repeat (CRISPR)-associated protein 9 nuclease (Cas9) (Arun et al., 2018). ASO is an ideal approach for achieving effective lncRNA knockdown that can exert noteworthy inhibitory effects on tumor growth and progression (Crooke, 2017). One of the major advances in ASO chemistry is the development of locked nucleic acid (LNA) (Vester and Wengel, 2004) that is synthesized using modified RNA nucleotides. Recently, the antimetastatic effect of MALAT1 targeting by ASO was reported in a lung cancer xenograft model, highlighting the potential use of ASO as a promising therapeutic approach for targeting lncRNA (Gong et al., 2019). On the other hand, transcriptional silencing of lncRNA using CRISPR-based approaches is also feasible. Indeed, the recently identified CRISPR-Cas13 system represents another promising approach for lncRNA knockdown (Abudayyeh et al., 2017). The good news is that sequence-based nucleic acid therapeutics are evolving at a rapid pace and more potential approaches could be identified in the future (Gudenas et al., 2019).

7 Effect of LINC00152 on the radiosensitivity of NSCLC cells

Irradiation reduces the viability of lung cancer cells and induces apoptosis in a dose-dependent manner. Overexpression of LINC00152 can restore the decrease of cell viability and inhibit irradiation-mediated cell apoptosis through direct binding to miR-195 (Zhang and Li, 2018). Indeed, the expression levels of LINC00152 in NSCLC tissues and cells were upregulated after radiation and were negatively correlated with miR-195 levels. Consequently, some target genes of miR-195, such as coactivator-associated arginine methyltransferase 1 (*CARM1*), Yes-associated protein 1 (*YAP*), glycerophosphodiester phosphodiesterase domain containing 5 (*GDPD5*), and Wnt family member 3A (*WNT3A*), were significantly increased. In contrast, LINC00152 suppression in A549 and 95D lung cancer cells induced the expression of miR-195 and reduced the expression of its target genes. Additionally, transfection of miR-195 inhibitor reversed the favorable changes on cell biological behavior caused by LINC00152 knockdown, such as radiosensitivity. These results further support the oncogenic behavior of LINC00152 in NSCLC.

Chemotherapeutic and targeted drug resistance has always been the dilemma facing clinical treatment. It has been reported that LINC00152/miR-193a-3p/ERBB4/AKT axis can regulate the sensitivity of colon cancer cells to oxaliplatin (L-OHP) treatment (Yue et al., 2016). On the other hand, LINC00152/miR-139-5p/NOTCH1 was shown to influence 5-fluorouracil resistance in colon cancer (Bian et al., 2017). Interestingly, LINC00152 expression in doxorubicin-resistant MCF-7 breast cancer cells was significantly higher than that in the parental cells (Hu et al., 2018). Decreasing LINC00152 expression promoted chemosensitivity to temozolomide and enhanced survival of patients with high-grade glioma (Wang W et al., 2018). These results indicate that LINC00152 can serve as a predictor of chemoresistance. However, there is currently no report on the effect of LINC00152 on lung cancer chemotherapy or molecule-targeted therapy. Whether LINC00152 plays a regulatory role in the drug resistance of lung cancer is to be determined.

8 Bioinformatics analysis on LINC00152 in lung cancer

Xu et al. (2017) analyzed data from the TCGA and GEO databases. They found that LINC00152 is highly expressed and associated with poor prognoses

in bladder, cervical, colon, renal, liver, lung, and other cancers. They explored the relationship between LINC00152 expression and histone modification using the encyclopedia of DNA elements (ENCODE) database (Davis et al., 2018). Among 15 tumor cell lines, including lung cancer, LINC00152 was regarded as a promoter-like lncRNA because its transcription initiation site had an H3K4me3/H3K4me1 value of >1.2. Furthermore, they demonstrated that LINC00152 promoted tumor cell proliferation, invasion, and apoptosis by binding to EZH2 in vitro and in vivo. Reon et al. (2018) analyzed the expression of LINC00152 in all tumor samples in the TCGA database, with their matched normal controls, which showed that LINC00152 was highly expressed in almost all tumor samples. High LINC00152 expression was associated with poor prognosis of head and neck squamous cell carcinoma, lung adenocarcinoma, renal clear cell carcinoma, etc. Feng et al. (2017) extended the analysis of LINC00152 expression using RNA-Seq data of 6220 cancer cases from the MiTranscriptome database. High expression of LINC00152 was observed in multiple types of tumors, including lung squamous cell carcinoma and large cell lung cancer, which further confirms that LINC00152 can serve as a tumor biomarker or potential therapeutic target in the future.

9 Conclusions and perspectives

The experimental research on LINC00152 in NSCLC is still scarce and the effect of LINC00152 in NSCLC has not been fully elucidated (Fig. 1). However, the long-established function of LINC00152 in other cancers suggests a potential role for LINC00152 in NSCLC (Zhou et al., 2015; Teng et al., 2017; Su et al., 2018).

Chen et al. (2017) showed that, even in the same type of tumor cell lines, the subcellular localization and expression of LINC00152 are heterogeneous. Thus, it is difficult to give a clear conclusion on the sub-cellular location of LINC00152. On the one hand, the heterogeneous LINC00152 expression can be used as a profitable condition to study the effect of LINC00152 up- or down-regulation in the corresponding cell lines. On the other hand, it can also reveal the complexity of LINC00152 mechanisms, which greatly influences research effort.

It has been shown that LINC00152 is adjacent to another lncRNA on chromosome 2 (chr2), MIR4435-2 host gene (MIR4435-2HG); LINC00152 is located on chr2 at 87455476–87606739, while MIR4435-2HG is located on chr2 at 111196350–111495115 (Nötzold et al., 2017; Reon et al., 2018). Interestingly, the sequences of the two lncRNA strands differ only by 6 bases, and they both contain the M8 sequence. In glioma cells, the expression levels of LINC00152 and MIR4435-2HG were identical. Targeting LINC00152 by siRNA simultaneously down-regulated the expression of LINC00152 and MIR4435-2HG, which suggests that these two lncRNAs might have common regulatory effects. Meanwhile, MIR4435-2HG is a host gene for miR-4435 that is transcribed from a MIR4435-2HG intron (Reon et al., 2018). In fact, this raises concerns about finding from multiple previous studies. For example, it raises concerns about the sequence specificity and efficiency of LINC00152 PCR and siRNA primers. Such problems should be fully considered in future studies.

At present, almost all studies on LINC00152 have been performed in China. Verification on tumor tissue and blood samples also poses some problems such as relatively small sample size and lack of consensus on detection standard (Yang et al., 2016). In the future, it would be necessary to develop uniform testing procedure, expand the sample size, and construct multi-center cooperations. Nevertheless, the current attempts offer the opportunity to study lung cancer pathogenesis and progression. In this regard, interpreting the orchestrated regulatory network of lncRNAs would be helpful in elucidating novel diagnostic and therapeutic targets to improve clinical outcomes.

Contributors

Hong YU and Shu-bin LI wrote, edited, and revised the manuscript. Both authors have read and approved the final manuscript.

Compliance with ethics guidelines

Hong YU and Shu-bin LI declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by either of the authors.

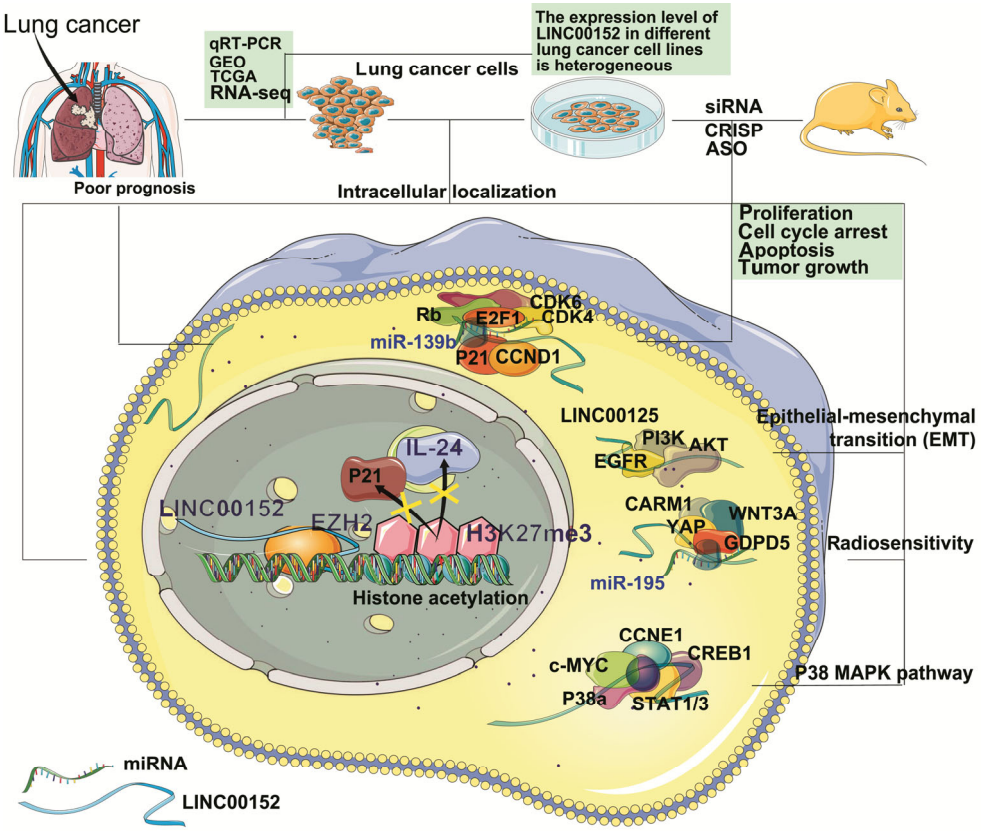

Fig. 1 Potential mechanisms of LINC00152 in NSCLC

LINC00152 has been associated with poor prognosis of non-small cell lung cancer (NSCLC) patients. It has been shown to be highly expressed in tumor tissues and peripheral blood samples of NSCLC patients through analysis of the data from quantitative real-time polymerase chain reaction (qRT-PCR) assay, RNA sequencing (RNA-seq), The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO) databases. In vitro, the expression level of LINC00152 in different NSCLC cell lines is heterogenous. It is located in both cytoplasm and the nucleus, and it can exert carcinogenic effects through different molecular mechanisms. In the nucleus, LINC00152 regulates gene expression by binding to enhancer of zeste homolog 2 (EZH2), while it affects cellular signaling cascades in the cytoplasm. It can also bind specific microRNAs (miRNAs) as competing endogenous RNA (ceRNA) to regulate the expression of target messenger RNAs (mRNAs). On the other hand, the mechanisms of LINC00152 can be studied in vivo by regulating its expression using small interfering RNA (siRNA), clustered regularly interspaced short palindromic repeat (CRISPR), and antisense oligonucleotide (ASO) approaches in xenograft models. CDK: cyclin-dependent kinase; E2F1: E2F transcription factor 1; CCND1: cyclin D1; PI3K: phosphoinositide-3-kinase; EGFR: epidermal growth factor receptor; CARM1: coactivator-associated arginine methyltransferase 1; WNT3A: Wnt family member 3A; YAP: yes-associated protein 1; GDPD5: glycerophosphodiester phosphodiesterase domain containing 5; CCNE1: cyclin E1; CREB1: cyclic adenosine monophosphate (cAMP)-responsive element binding protein 1; STAT1/3: signal transducer and activator of transcription 1/3

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中文概要

题　目：LINC00152 在非小细胞肺癌中的作用

概　要：非小细胞肺癌（NSCLC）约占所有肺癌病例的85%，其发生发展过程涉及复杂的基因调控网络，其中除了编码基因，还包括大量不同类型的非编码 RNA，如长链非编码 RNA（lncRNA）。lncRNA 在人类癌症中的作用正在被深入研究，在 NSCLC 中的作用也日益受到关注。最近，在不同类型的肿瘤中发现了一个新的致癌 lncRNA：LINC00152（又被称为细胞骨架调节 RNA）。LINC00152 在 NSCLC 患者的肿瘤组织和外周血中高表达，并与患者的不良预后相关。上调 LINC00152 表达已被证实在体外能促进 NSCLC 细胞的增殖、侵袭和迁移，并且在体内能促进裸鼠移植瘤的生长。本文综述了 LINC00152 在 NSCLC 中的作用及其机制。

关键词：长链非编码 RNA；LINC00152；非小细胞肺癌；增殖；预后