

## Emerging Role of Long Non-Coding RNAs in Non-Small Cell Lung Cancer: Progress and Prospects

WeiJun Wu<sup>1</sup>, Jieqing Zhao<sup>2</sup> and Yongsheng Wang<sup>3\*</sup>

<sup>1</sup>Department of Clinical Pharmacy, Nanjing Drum Tower Hospital Affiliated to Medical School of Nanjing University, Nanjing, PR China

<sup>2</sup>Department of Clinical Pharmacy, Nanjing Xianlin Drum Tower Hospital, Nanjing, PR China

<sup>3</sup>Department of Respiratory Medicine, Nanjing Drum Tower Hospital Affiliated to Medical School of Nanjing University, Nanjing, PR China

\*Corresponding author: Yongsheng Wang, Department of Respiratory Medicine, Nanjing Drum Tower Hospital Affiliated to Medical School of Nanjing University, Nanjing, 210008, PR China, Tel: 86-025-83106666; Fax: 86-025-68183333; E-mail: dolphin8012@yahoo.com

Received date: January 09, 2017; Accepted date: January 23, 2017; Published date: January 28, 2017

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### Abstract

Non-small cell lung cancer (NSCLC), accounts for approximately 80-85% of all lung cancer cases, is the most common cause of cancer-related death worldwide. With the advances of high-throughput sequencing, accumulating evidence suggested that the long non-coding RNA molecules, with transcripts larger than 200 nucleotides, have important roles in multiple biological processes in NSCLC. In this review, we will highlight the emerging roles of long non-coding RNAs (lncRNAs) in NSCLC, discussing both onco-lncRNAs and tumor-suppressor lncRNAs, and their potential clinical applications as diagnostic and therapeutic targets in NSCLC.

**Keywords:** NSCLC; Long noncoding RNAs; Biomarkers; Gene therapy

### Introduction

Lung cancer comprises non-small cell lung cancer (NSCLC) and small cell lung cancer, and NSCLC accounts for approximately 85% of all lung cancer cases [1]. It continues to be the leading cause of cancer-related death among men and women [2]. Advances in molecular diagnostics and immunotherapeutic have propelled the rapid development of novel treatment agents for NSCLC in recent years, however, the prognosis are far from satisfactory and survival time is still low [3,4]. Therefore, comprehensive understanding of the molecular mechanisms and pathways that underlying NSCLC tumorigenesis and progression is essential for achieving early diagnosis and better treatment outcome for NSCLC.

Investigation into the molecular pathogenesis of tumorigenesis has usually focused on protein-coding genes. Recent evidence from the advance of high-resolution microarray and genome-wide sequencing technology demonstrated that 98% of human genome DNA is non-protein coding, comparing to only 2% of the human genome protein-encoding [5]. lncRNAs are usually more than 200 nucleotides (nt) in length, and this length distinguishes lncRNAs from small regulatory RNAs such as microRNAs, small nucleolar RNAs, piwi-interacting RNAs, short interfering RNAs, and other short RNAs [6]. lncRNAs have been reported to be involved in multiple biological processes such as development and progression of human malignancies [7,8]. Although the potential functions of lncRNAs are still enigmatic in NSCLC, an increasing number of studies have now demonstrated that lncRNAs play a major role in development and progression of NSCLC [9-11].

The origin of lncRNAs is not clear yet. Derrien et al. suggested that lncRNAs can be classified into three subtypes based on genomic location, lncRNAs intronic (transcribed from the introns of coding genes), intergenic (transcribed from the regions between two

contiguous coding genes) and antisense lncRNAs (transcribed from the opposite strand of coding genes) [12]. Originally considered as a transcriptional noise, lncRNAs are conversely tightly regulated and highly tissue specific. Furthermore, recent data demonstrates that lncRNAs can regulate genes via transcriptional, post-transcriptional and epigenetic mechanisms [13]. Accumulating evidence shows that some lncRNAs play roles as onco-lncRNAs, such as metastasis-associated-in-lung-adenocarcinoma-transcript-1 (MALAT1), HOX antisense intergenic RNA (HOTAIR), colon cancer-associated transcript 2 (CCAT2), lncRNA H19 (H19), plasmacytoma variant translocation 1 (PVT1), antisense noncoding RNA in the INK4 locus (ANRIL), urothelial carcinoma-associated 1 (UCA1), distal-less homeobox 6 antisense 1 (DLX6-AS1) and some play part as tumor-suppressor lncRNAs such as forkhead box F1 antisense 1 (FOXF1-AS1), SPRY4 intronic transcript 1 (SPRY4-IT1), maternally expressed gene 3 (Meg3), BRAF activated noncoding RNA (BANCR), growth arrest specific gene 6 (GAS6), growth arrest-specific transcript 5 (GAS5), promoter of CDKN1A antisense DNA damage-activated RNA (PANDAR). In this review, we intend to summarize the emerging roles of lncRNAs in NSCLC based on their role as onco-gene or tumor suppressor gene, and will evaluate their future opportunities and challenges in diagnostics and therapy of NSCLC patients.

### Onco-lncRNAs

#### MALAT1

MALAT1, one of the first discovered cancer-associated lncRNAs, is a highly conserved nuclear ncRNA and a prognostic marker for metastasis and patient survival in NSCLC, specifically in early stages of lung adenocarcinoma [14]. MALAT1 was demonstrated to be associated with cell migration and metastasis by inducing epithelial-mesenchymal transition (EMT), and to regulate the expression of metastasis-associated genes [15]. Gutschner et al. unraveled the active function of MALAT1 as a regulator of gene expression governing hallmarks of lung cancer metastasis in their loss-of-function model

[16]. And Ji et al. demonstrated that NSCLC patients with high MALAT1 expression were at high risk to develop metastasis in early-stage [14]. Shen et al. showed that MALAT1 promotes lung cancer brain metastasis by inducing EMT [17]. MALAT-1 expression levels were associated with patient survival and tumor-promoting functions of MALAT-1 was found using overexpression and RNA interference

(RNAi) approaches in A549 cell lines [18]. Tripathi et al. suggested that MALAT1 controls cell cycle progression by regulating the expression of oncogenic transcription factor B-MYB [19]. These data suggested that MALAT1 play a role in NSCLC as onco-gene and could serve as a potential therapeutic target (Table 1).

Long Noncoding RNAs	Length (kb)	Function in NSCLC	Molecular mechanism	References
MALAT1	8	Oncogenic	Epithelial mesenchymal transition facilitation Regulation of bcl-2, CTHRC1, CCT4, HMMR and ROD1 in MAPK signaling	Ji et al. [14], Shen et al. [17], Schmidt et al.[18], Gutschner et al. [16], Tripathi et al. [19]
HOTAIR	2.2	Oncogenic	Regulation of cell migration and anchorage-independent cell growth Regulation of cell invasion and metastasis	Nakagawa et al. [22], Liu et al. [23]
CCAT2	0.34	Oncogenic	Promote invasion of NSCLC and a biomarker for lymph node metastasis	Qiu et al. [25]
H19	2.3	Oncogenic	Regulation of C-myc signaling, p53 signaling pathways and miR-107 Regulation of cell migration and invasion	Wang et al. [27], Cui et al. [28], Zhang et al. [29]
PVT1	300	Oncogenic	Regulation of cell proliferation through epigenetically regulating LATS2 expression Promote tumorigenesis	Wan et al. [31], Cui et al. [32], Yang et al. [33]
ANRIL	3.9	Oncogenic	Regulation of C-myc signalling Promote cell proliferation and inhibit apoptosis by silencing KLF2 and P21 expression.	Lu et al. [8], Nie et al. [34], Naemura et al. [35]
UCA1	1.4	Oncogenic	Regulation of mTOR/Akt pathway ERBB4 upregulation	Cheng et al. [37], Nie et al. [38]
DLX6-AS1	5.8	Oncogenic	JAK/STAT upregulation	Li et al. [39]

**Table 1:** List of main NSCLC-associated oncogenic long noncoding RNA.

## HOTAIR

HOTAIR (HOX transcript antisense intergenic RNA) has been implicated in several cancers, and plays a role as an oncogenic factor in different cancer cells, such as breast, gastric, and colorectal cancer cells [20,21]. Nakagawa et al. showed that HOTAIR-expressing A549 cells induced cell migration and anchorage-independent cell growth in vitro, which indicated the expression of HOTAIR enhanced the aggressive behavior of NSCLC cells [22]. Liu et al. indicated that HOTAIR was significantly up-regulated in NSCLC tissues and regulate NSCLC cell invasion and metastasis, partially via the down-regulation of HOXA5 [23]. Thus, HOTAIR may represent a potential therapeutic target for NSCLC treatment and as a new biomarker of poor prognosis.

## CCAT2

CCAT2 (colon cancer-associated transcript 2) is a recently discovered lncRNA in colon cancer, which was associated with tumor growth, metastasis, and chromosomal instability [24]. Qiu et al. indicated that CCAT2 was a lung adenocarcinoma-specific lncRNA and promotes invasion of NSCLC and could be regarded as a biomarker for lymph node metastasis [25].

## H19

H19, the first identified imprinting lncRNA, plays a critical role in tumorigenesis [26]. In NSCLC, H19 exhibits oncogenic function and is involved in tumor development. Wang et al. found that H19 plays an important role in the migration and invasion of NSCLC by regulating MACC1, EGFR,  $\beta$ -catenin and ERK1/2 [27]. H19 promoted cell cycle progression of non-small cell lung cancer via down-regulation of miR-107 [28]. Zhang et al. demonstrated that H19 is involved in the oncogenesis of NSCLC, and H19 may be a potential diagnostic and target for new therapies in patients with NSCLC [29].

## PVT1

PVT1 oncogene, was found to be up-regulated in a large variety of human tumors, could promote cell proliferation, cell cycling, and the acquisition of stem cell-like properties [30]. Wan et al. demonstrated that PVT1 regulates cell proliferation through epigenetically regulating LATS2 expression [31]. Cui et al. showed that PVT1 could promote the proliferation of NSCLC cells by down-regulating p15 and p21 expression [32]. Yang et al. indicated that lncRNA PVT1 is significantly up-regulated in NSCLC tissues and might serve as a

promising biomarker for diagnosis, prognosis and potential therapeutic target of NSCLC [33].

## ANRIL

LncRNA ANRIL has been demonstrated to exert oncogenic activity in a variety of carcinomas in NSCLC. Lu and colleagues [8] suggested that ANRIL was positively correlated with advanced tumor-node-metastasis stage and greater tumor diameter, through physical interaction between c-Myc and ANRIL. Nie et al. showed that ANRIL expression was increased in NSCLC tissues, and patients with high levels of ANRIL expression had a relatively poor prognosis [34]. Naemura et al. indicated that ANRIL positively regulates the proliferation of cancer cells via regulating p15 [35]. Together, ANRIL is involved in the oncogenesis of NSCLC

## UCA1

UCA1 (Human urothelial Carcinoma Associated 1), an lncRNA was first identified in human bladder carcinoma with oncogenic activity [36]. Cheng et al. showed that UCA1 induced NSCLC cancer cells acquired resistance to EGFR-TKIs by activating the AKT/mTOR pathway and EMT [37]. A recent study from Nie found that LncRNA-UCA1 exerts oncogenic functions in NSCLC by targeting miR-193a-3p [38].

## DLX6-AS1

DLX6-AS1 (distal-less homeobox 6 antisense 1) was identified from microarray analysis. It was up-regulated in NSCLC tissues, and high DLX6-AS1 expression levels were significantly associated with both histological differentiation and TNM stage [39].

## Tumor-Suppressor lncRNAs

### FOXF1-AS1

FOXF1-AS1 (forkhead box F1 antisense 1) was a newly discovered lncRNA in NSCLC. Our previous study demonstrated that the

expression of FOXF1-AS1 was significantly down-regulated in lung cancer using GeneChip® Human Gene 2.0 ST Array. FOXF1-AS1 was associated with lung cancer cell migration and invasion by regulating EMT. Interestingly, we also found that FOXF1-AS1 might regulate EMT, stemness and metastasis of NSCLC cells via EZH2, indicating it as a therapeutic target for future treatment of NSCLC [11].

### SPRY4-IT1

LncRNA SPRY4-IT1 (SPRY4 intronic transcript 1) derived from an intron within SPRY4, is transcriptionally repressed by EZH2. SPRY4-IT1 was previously reported to be up-regulated in melanoma cells [40]. Sun et al. showed that SPRY4-IT1 affects NSCLC cell proliferation and metastasis partly via the epithelial mesenchymal transition (EMT), and SPRY4-IT1 plays as regulators of NSCLC pathogenesis, and may facilitate the development of lncRNA-related diagnostics and therapeutics [9].

### Meg3

Meg3 (maternally expressed gene 3) expresses in many normal tissues. Meg3 represents as a tumor suppressor gene, and its ectopic expression can inhibit cell proliferation and promote cell apoptosis in human glioma cell lines [41]. Lu et al. findings indicated that MEG3 is significantly down-regulated in NSCLC tissues that could be affected by DNA methylation, and regulate NSCLC cell proliferation and apoptosis, partially via the activation of p53. MEG3 may represent a novel biomarker of the poor prognosis and is a potential therapeutic target for NSCLC [42]. In another study, suggested that Meg3 and miR-3163 may coordinate suppression of translation of Skp2 mRNA in NSCLC cells to inhibit NSCLC cell growth [43].

Long Noncoding RNAs	Length (kb)	Function in NSCLC	Molecular mechanism	References
FOXF1-AS1	3	Tumor suppressor	Epithelial mesenchymal transition inhibition via EZH2	Miao et al. [11]
SPRY4-IT1	1.8	Tumor suppressor	Promote NSCLC cell proliferation and metastasis via EZH2	Sun et al. [9]
MEG3	1.6	Tumor suppressor	p53 upregulation Regulation of Skp2 in NSCLC by miR-3163 require coordination of Meg3	Lu et al. [42], Su et al.[43]
BANCR	0.69	Tumor suppressor	Epithelial mesenchymal transition inhibition E-cadherin, N-cadherin and vimentin gene expression modulation	Sun et al. [45]
GAS6-AS1	44	Tumor suppressor	Regulation of SLUG expression, via JNK and ERK1/2 signaling	Han et al. [46]
GAS5-AS1	0.65	Tumor suppressor	p53-induced DNA damage response and apoptosis, mTOR inhibition Promote tumor metastasis via upregulation of EMT markers	Shi et al. [47], Wu et al. [48]
PANDAR	1.5	Tumor suppressor	Bcl-2 downregulation	Han et al. [50]

**Table 2:** List of main NSCLC-associated tumor suppressor long noncoding RNA.

## BANCR

BANCR (BRAF activated noncoding RNA), an 693-bp lncRNA on chromosome 9, is over-expressed in melanoma cells and crucial for melanoma cell migration [44]. And in NSCLC, Sun and colleagues indicated that BANCR actively functions as a regulator of EMT during NSCLC metastasis, suggesting that BANCR could be a biomarker for poor prognosis of NSCLC [45].

## GAS6-AS1

lncRNA GAS6-AS1 (growth arrest specific gene 6) is located at 13q34 and on the downstream side of GAS6 (originally regarded as a gene induced in cells during growth arrest) and is transcribed from the antisense direction of GAS6 [46]. Han et al. showed altered lncRNA GAS6-AS1 expression might be involved in the development and progression of NSCLC by influencing its host gene and may serve as a potential diagnostic biomarker in patients with NSCLC [46].

## GAS5 and GAS5-AS1

lncRNA GAS5 (growth arrest-specific transcript 5) (exon 12-derived sequence) is firstly found to be up-regulated during growth arrest induced by serum starvation or the lack of growth factors. Shi et al. suggested that GAS5 is a tumor suppressor in NSCLC, and the function of GAS5 is mediated by p53-dependent and p53-independent pathways [47]. And another recent study demonstrated that histone modifications lead to epigenetic silencing of GAS5-AS1 in NSCLC and subsequently promote tumor metastasis via up-regulation of several key EMT markers [48]. Together, GAS5 and GAS5-AS1 could represent a potential diagnostic marker for NSCLC and a novel therapeutic target in patients with NSCLC (Table 2).

## PANDAR

lncRNA PANDAR (promoter of CDKN1A antisense DNA damage-activated RNA) was firstly reported by Hung et al. to be induced by DNA damage in a p53-dependent manner [49]. Han et al. showed that PANDAR was involved in the progression of NSCLC through the p53/PANDAR/NF-YA/Bcl-2 interaction, suggesting it might serve as therapeutic target for NSCLC [50].

## Concluding Remarks and Future Perspectives

The morbidity and mortality rates of NSCLC are raising rapidly compared with other malignant tumors. Intriguingly, most of NSCLC related deaths are because of secondary site metastases. Previous studies of mechanisms underlying metastasis are mostly focused on protein coding genes. Given the fact that 80% of the genome is transcribed into RNA but less than 2% is translated into proteins, these non-coding RNAs, including lncRNAs possess fundamental roles in tumor biology. In present review, we give a brief description of the current understanding of lncRNAs in human NSCLC. However, more researches still needed to extend our understanding of lncRNAs in NSCLC, facilitating to improve early diagnostic accuracy and overall survival of NSCLC patients in a foreseeable future.

## Acknowledgments

This work has been supported by Natural Science Foundation of China (NO. 81301882).

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