Review

The Emerging Role and Promise of Long Noncoding RNAs in Lung Cancer Treatment

Ying Chen Chen Li Yan Pan Siqi Han Bing Feng Yanping Gao Jing Chen
Kai Zhang Rui Wang Longbang Chen

Department of Medical Oncology, Jinling Hospital, School of Medicine, Nanjing University, Nanjing, China

Key Words

Long noncoding RNA • Lung cancer • Biomarker resistance

Abstract

Lung cancer is the leading cause of cancer death around the world. The advanced discovery of numerous long noncoding RNAs (lncRNAs) has dramatically changed the understanding of biology of human cancers, including lung cancer. lncRNAs are a group of noncoding RNAs (ncRNAs) with a length greater than 200 nucleotides with limited or no protein-coding capacity. Increasing evidence has shown that specific lncRNAs may be implicated in the process of tumorigenesis. Because of their roles in the regulation of multiple molecular pathways associated with changes in gene expression, lncRNAs can serve as potential diagnostic biomarkers or therapeutic targets in lung cancer. Importantly, dysregulated lncRNAs is reported to be correlated with the sensitivity of lung cancer cells to anticancer therapies, including chemotherapy, molecular-targeted therapy, etc. Herein, we review the recent progress of lncRNAs in lung cancer, with a particular focus on the multiple molecular roles of regulatory lncRNAs on the molecular signaling pathways involved in tumorigenesis and the resistance to such therapies.

© 2016 The Author(s)
Published by S. Karger AG, Basel

Introduction

Lung cancer remains the most common cancer deaths worldwide and accounts for 19.4 % of total cancer mortality [1]. In industrialized countries, lung cancer is the leading cause of cancer death in males and is growing in incident rates among females [2]. More than half of all patients diagnosed with lung cancer are poor prognosis. Despite improvements in early diagnosis, advancements in treatment, five year survival rate for primary lung cancer remaining below 16% [3].

Rui Wang, MD

Department of Medical Oncology, Jinling Hospital, School of Medicine, Nanjing University, Nanjing, Jiangsu 210002, (China)
Tel. +86-25-80860072, Fax +86-25-80860072, E-Mail wangrui1977218@163.com

Primary lung cancers are traditionally classified as either small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC). NSCLC accounts for approximately 80% of all primary lung cancers with adenocarcinoma, squamous cell carcinoma and large cell carcinoma constituting the major histological types. At the time of diagnosis, almost half of NSCLC cases are localized or locally advanced, complete surgical resection remains the best option for these patients. However, for patients with advanced NSCLC, platinum-based combination chemotherapy is currently recommended as the standard treatment. With the increase in understanding of the biological mechanisms in lung cancer, molecular targeting treatment has achieved graveness progression and the curative effect was striking. The epidermal growth factor receptor (*EGFR*) is seen as a promising target and frequently mutated in patients with NSCLC. *EGFR*-directed therapies and angiogenesis inhibitors have now emerged as the best options for these patients with a mutation in exons 19 or 21 of the *EGFR* [4]. In contrast, 80% of patients with SCLC have metastatic disease at the time of diagnosis. SCLC is characterized by rapid growth rate, early regional lymph node metastasis, and spread to distant sites. Survival percentages for lung cancer is significantly low when only SCLC is considered [5]. For prognostic and therapeutic reasons, having a standardized and validated approach to stage the disease accurately is imperative.

Due to the development of resistance to therapies, the treatment of lung cancer faced a significant challenge [6]. Cancer drug resistance can be classified in two types: pre-existing and acquired [7]. Recent studies have demonstrated that intracellular signaling pathways play key physiological roles and the abnormal activation of signaling pathways may be correlated with acquired resistance. For example, *RUNX3* confers, at least in part, resistance of lung adenocarcinoma cells to docetaxel (DTX) agent via activating AKT signaling [8]. In addition, dysregulated of *ZEB1* and *ING4* is also found to be involved in the resistance of lung adenocarcinoma cell to DTX [9, 10]. Meanwhile, the dysregulation of ncRNAs has been highlighted as a novel mechanism of resistance in recent years.

LncRNAs biogenesis and gene expression

Over the last decade, advances in genome-wide analysis of gene expression have revealed that protein coding gene exons constitute less than 3% of the human genome, and a growing list of noncoding RNA genes within introns has been shown to regulate the expression of genes [11]. The ncRNAs composes three types: long ncRNAs, mid-size ncRNAs and short ncRNAs. Recently, the research of short ncRNAs has been the hotspot, such as microRNAs (miRNAs). MiRNAs are exciting molecular entities with additional advantages as targeting gene regulation to change the lung cancer treatment in the future. The association between altered let-7 family expression and the biological and clinical effects in lung cancer was first reported. Further study has found that restoration of Let-7c can reverse chemo- or radioresistance of lung adenocarcinoma cell via targeting Bcl-xL [12]. MiR-145 and miR-224 are reported to confer the chemoresistance of lung adenocarcinoma cells to cisplatin (CDDP) via delaying the progression of the cell cycle from G1 to S phase [13, 14]. In addition, miR-650 has been shown as a potential target for chemosensitizing lung adenocarcinoma cells to DTX and of interest, miR-451 play a role in both DTX or CDDP resistance and radioresistance [15, 16]. These results clearly suggest that dysregulation of miRNAs is associated with the resistance of lung cancer to anti-cancer therapies have been reported. LncRNA, another novel class of ncRNA, is rapidly gained prominence and gives hope for a more profound understanding of lung cancer [17].

In general, lncRNAs are greater than 200 nucleotides with limited or no protein-coding capacity. In contrast to protein-coding genes, the transcription start sites of lncRNAs are around by a higher level of DNA methylation independent of their expression status, which makes a clear distinction between the two [18]. Transcription of lncRNAs occurs from an independent gene promoter and a large number of them are transcribed by RNA polymerase II. The act of some transcription is associated with epigenetic signatures common to protein-

coding genes, such as trimethylation of histone 3 lysine 4 (H3K4me3) at the transcriptional start site and trimethylation of histone 3 lysine 36 (H3K36me3) throughout the gene body. The expression levels of many identified lncRNA appear to be lower than protein-coding genes, and some lncRNAs are frequently expressed in a tissue-specific manner [19].

Up to now, more than 3000 lncRNAs have been identified. It is not easy to generate comprehensive classifications of lncRNAs, because the same lncRNAs may be listed in different groups in all classifications. Derrien et al. subclassified lncRNAs according to their location with respect to the nearest protein-coding gene, and the categories include exonic lncRNAs (antisense/sense), intronic lncRNAs (antisense/sense), overlapping lncRNAs (antisense/sense), and intergenic lncRNAs [20]. As localized to the nucleus, lncRNAs have the potential capabilities of modulating chromatin or functioning as genetic expression regulators. Aberrant expression of several lncRNAs is related to carcinogenesis, and dysregulation of them participate in tumor initiation, progression, and metastasis in various types of human cancers, such as gastric cardiac adenocarcinoma, breast cancer, hepatocellular carcinoma, etc [21-23]. LncRNAs regulate various molecular signaling pathways via changing gene expression, and therefore, dysregulation of their expression may be implicated in general mechanisms of carcinogenesis [24]. The expression level of lncRNAs has indeed shown significantly different between cancer tissues and normal tissues. HOTAIR (HOX transcript antisense RNA), MALAT1 (metastasis associated lung adenocarcinoma transcript 1), HOTTIP (HOXA transcript at the distal tip), ANRIL (antisense noncoding RNA in the INK4 locus), and ZNF2 have been found to be upregulated in lung cancer tissues, and upregulation of those lncRNAs is correlated with higher TNM stage, advanced lymph-node metastasis, and poorer overall survival of patients [25-30]. Meanwhile, plenty of tumor suppressive lncRNAs have been identified, such as MEG3 (maternally expressed gene 3), lincRNA-p21, GAS5 (growth arrest specific transcript 5), TUG1 (taurine-upregulated gene 1) [31-33]. Considering their roles in carcinogenesis, lncRNAs may hold promise as diagnostic or prognostic biomarkers for lung cancer [34].

Roles of lncRNAs in lung cancer biology

LncRNAs play important roles in many biological processes, such as transcription, splicing, translation, protein localization, epigenetic gene expression, ribonucleoprotein complexes, chromatin modifying enzymes, and so on [35-37] (Fig. 1). Because of their roles in the regulation of multiple molecular signaling pathways associated with changes in gene expression, lncRNAs are implicated in cancer progression implicated in the initiation and progression of lung cancer [38]. For example, MALAT1 is the first identified lung cancer-associated lncRNA, which promotes motility and proliferation of lung cancer cells by regulating caspase-8, caspase-3, BAX, BCL-2, and BCL-XL [39]. In the past decade, the increasing recognition of lncRNAs has defined these genes as critical actors in numerous cellular processes of lung cancer [40].

Fig. 1. The molecular mechanisms involved in action of lncRNAs. (A) LncRNAs can guide chromatin modifying enzymes to specific genomic loci target genes. (B) LncRNAs can bind to the promoter of genes and regulate their expression to mediate transcription pathway. (C) LncRNAs can recruit multiple proteins to form ribonucleoprotein complexes. (D) Some lncRNAs can be processed to miRNAs, or they can function as decoy for miRNA target sites. (E) LncRNAs can affect the stability of mRNAs via binding to its target mRNAs.

Fig. 2. Regulatory networks of special lncRNAs involved in the pathogenesis of lung cancer. (A) LncRNAs related to cell proliferation and survival pathways. (B) LncRNAs related to cell invasion and metastasis. (C) LncRNAs related to cell apoptosis.

LncRNAs related to cell proliferation

Multiple signaling pathways are activated and contribute to tumor cell survival and proliferation. To date, there are a number of research findings alluding to lncRNAs and cell proliferation in different cancer types, including lung cancer (Fig. 2A). Numerous lncRNAs have been reported as inducer of uncontrolled cell proliferation in lung cancer. Some of these examples include PANDAR (promoter of CDKN1A antisense DNA damage-activated RNA), which is demonstrated to repress the proliferation *in vitro* and *in vivo* of NSCLC cells when overexpressing [41].

Further experiments revealed that TUG1 (taurine-upregulated gene 1) is a direct transcriptional target of *p53*. *P53*-regulated TUG1 is a growth regulator, which can bind to PRC2. Also, the promoter of *HOXB7* locus could be bound by EZH2 (enhancer of zeste homolog 2), a key component of PRC2, suggesting that *HOXB7* is a bona target of TUG1/PRC2-regulated genes. This TUG1-mediated growth regulation is in part due to specific modulation of *HOXB7*, thus participating in AKT and MAPK pathways [33]. ANRIL, a lncRNA located in cell nucleus and silences *KLF2* and *P21* by directly binding with EZH2, could promote the proliferation of NSCLC cells [29]. Phospholipase D (PLD) produces phosphatidic acid (PA), and aberrant PLD/PA signaling has been observed in various types of human cancers. Kang and his colleagues showed that ANRIL was responsible in anti-tumorigenesis caused by PLD

inhibition, suggesting that combined incorporation of ANRIL into PLD inhibition-induced anti-tumorigenic signaling network could be a new effective therapeutic approach for controlling lung cancer [42].

Deng et al. found that depletion of HOTTIP not only caused cell cycle arrest in G0/G1 phase but also inhibited tumor growth in a mouse model of lung cancer, which were correlated with upregulation of cell cycle regulators Cdc25C, Cyclin B1 and Cyclin D1 [28]. Identical to HOTTIP, lncRNA AK001796 could regulate the expression of different cell-cycle-associated genes, including *BIRC5*, *TPDF2*, *CDC6*, *CDK5RAP1*, *GADD45A*, and *CCNC*. *TFDP2* encodes a protein that forms heterodimers with the E2F transcription factors, leading to the transcriptional activation of cell-cycle-regulated genes. *CDC6* regulates the early steps of DNA replication. *ATR* is a cell-cycle-checkpoint gene responsible for cell-cycle arrest and DNA damage repair in response to DNA damage. Reduced AK001796 potentially causes a cell-cycle arrest, with significant increases in the percentage of cells in G0/G1 in lung cancer cells [43]. *P27* as a tumor suppressor that regulates cell cycle proliferation can be a potential target of LUADT1 (lung adenocarcinoma transcript 1). Both *in vitro* and *in vivo* data showed that LUADT1 knockdown significantly inhibits cell proliferation and induces cell cycle arrest at the G0-G1 phase by epigenetically inhibiting the expression of *p27* [44, 45].

Functional validation shows that the most differentially expressed lncRNA across lung subtypes, LCAL1 (lung cancer associated lncRNA 1), contributes to cellular proliferation [46]. Furthermore, siRNA-mediated knockdown of MVIH could inhibit cell growth via regulating MMP-2 and MMP-9 protein expression in NSCLC [47]. Likewise, silencing of CCAT2 (Colon cancer associated transcript 2) could lead to inhibition of proliferation in NSCLC cell lines *in vitro* [48]. H19, a functional executor of oncogene *c-Myc* downstream, plays a key role in the development of lung cancer through affecting cell proliferation [49]. By contrast, MEG3 functions as a tumor suppressive lncRNA. Overexpression of MEG3 is found to induce the increased expression of MDM2 and p53 protein, and decreases NSCLC cells proliferation *in vitro* and impedes tumorigenesis *in vivo* [31]. These findings provide recent updates on the noncoding genetic targets for the prevention and treatment of lung cancer.

LncRNAs related to cell invasion and metastasis

Recent studies have demonstrated that abnormal expression of lncRNAs has been observed in tumor tissues, and dysregulation of numerous lncRNAs is correlated with poor prognosis in lung cancer. Studies examining the roles of lncRNAs in lung cancer development showed that ANRIL, HNF1A-AS1, PVT1, CARLo-5 and CCAT2 play important roles in migration and invasion in NSCLC cells [29, 48, 50-52]. In another study, *in vitro* experiments demonstrated that silencing of LINC01133 could significantly reduce the invasion ability of lung squamous cell cancer cells [53].

Elevated expression of lncRNA MALAT-1 has been observed in NSCLC, and are correlated with higher incidence of lymph node metastasis [54]. MALAT1, also known as NEAT2, is a highly conserved nuclear lncRNA and specifically enriched in nuclear speckles [55]. In lung cancer, MALAT1 actively regulates gene expression including a set of metastasis-associated genes independent of altering alternative splicing (Fig. 2B). It is known that aberrantly activated ERK/MAPK pathway contributes to cancer cell metastasis. Knockdown of MALAT-1 can downregulate the expression of MMP-9 and inactivate the extracellular signal-regulated kinase/ mitogen-activated protein kinase (ERK/MAPK) pathway. Also, lncRNA BCYRN1, which is the target of *c-MYC*, could increase the expression of MMP-9 and MMP-13 and then lead to the increased capacities of cell motility and invasiveness in NSCLC [56]. Additionally, MALAT-1 is reported to play an important part in TGF- β -induced EMT, which was a key step of cancer metastasis. Importantly, MALAT-1 could also regulate expression of several metastasis-associated genes including melanoma inhibitory activity 2 (*MIA2*, a negative regulator of tumor growth invasion), roundabout 1 (*ROBO1*, an inhibitor of glioma migration and invasion), glypican6 (*GPC6*, a promoter of breast cancer metastasis), ATP-binding cassette sub family A member 1 (*ABCA1*, an important factor for prostate cancer cell migration and epithelial-to-mesenchymal transition) [39]. Consequently, MALAT1 may

serve as an independent prognostic marker for patient survival and a potential therapeutic target in lung cancer.

Actin filament associated protein 1 antisense RNA1 (AFAP1-AS1) was reported to be the most significantly upregulated in lung cancer and associated with poor prognosis of patients. At the same time, *in vitro* functional experiments demonstrated that knockdown of AFAP1-AS1 significantly inhibited the invasive and migration capability of lung cancer cells by regulation of its antisense protein coding gene, actin filament associated protein 1 (AFAP1) and affecting the expression levels of several small GTPase family members and molecules in the actin cytokeleton signaling pathway [57].

HOTAIR, the lncRNA originally identified in breast cancer, was demonstrated to be upregulated in a variety of cancers including lung cancer. This lncRNA is a HOXC cluster-derived lncRNA that binds to the transcriptional co-repressor PRC2 and recruits PRC2 to silence its target genes. Recent studies have identified that HOTAIR has an oncogenic role both in SCLC and NSCLC, and consistent with these observations, upregulation of HOTAIR could enhance the aggressive behaviors of lung cancer cells [58, 59]. As the hypoxia-inducible lncRNA, HOTAIR is found to play an important role in hypoxia-enhanced aggressive phenotypes. HIF-1 α targets HOTAIR through direct interaction with putative HREs in the upstream region of HOTAIR in NSCLC cells, and it is conceivable that myc mediates activation of the HOTAIR gene by Col-1 [60]. Under normoxic conditions, HIF-1 α does not activate HOTAIR transcription, but *c-Myc* could be responsible for the transcriptional regulation of HOTAIR. Under hypoxic conditions, the hypoxia promotes *c-Myc* degradation and HIF-1 α could regulate HOTAIR expression, and then HOTAIR enhances cancer cell migration and invasion [61, 62]. HOXA5, a member of HOX family, has been reported to be involved in lung maturation and function. It was also found that inhibition of HOXA5 could significantly promote migration and invasion in A549 cells. In a study by Liu et al. showed that the oncogenic functions of HOTAIR may be partially exerted through downregulation of tumor suppressor *HOXA5* [63]. Furthermore, another study indicates that HOTAIR can promote gelatinase activity in lung cancer cells by promoting the activity of MMP-9 and/or MMP-2, consistent with a role in promoting invasion and metastasis [64].

LncRNAs related to cell apoptosis

The same lncRNAs may induce different biologies in cancer cells via regulating the expression of different target genes (Fig. 2C). For example, depletion of HOTTIP not only causes cell cycle arrest in G0/G1 phase, but also induces significant cell apoptosis [28]. Moreover, MEG3 stimulates *p53*-dependent transcription by driving transcription of the growth differentiation factor 15 (GDF15), but not that of *p21* [65, 66]. Thus, inhibition of lncRNA MEG3 leads to NSCLC cell proliferation and apoptosis, at least partially by preventing *p53* activation. *P53*, an important transcription factor, is capable of regulating the expression of many target genes and functioning as a tumor suppressor in tumor development. The mutation of *p53* is often found in most human cancers, including lung cancer [67]. In contrary, *p53* acts upstream of lncRNA Lnc_bc060912 in the regulatory network, and negatively regulates the expression of Lnc_bc060912, which represses cell apoptosis via interacting with the two DNA damage repair proteins PARP1 and NPM1 [68]. Also, overexpression of PANDAR significantly inhibits NSCLC cell growth *in vitro* and *in vivo* and enhances cell apoptosis partially via the transcriptional modulation of Bcl-2 by interacting with NF- κ B, suggesting that dysregulation of the *p53*/PANDAR/NF- κ B/Bcl-2 signaling axis might have a great effect on the progression and development of NSCLC [41].

LncRNAs related to lung cancer therapy resistance

LncRNAs related to cisplatin resistance in lung cancer

Cisplatin (CDDP) is a DNA-damaging cytotoxic agent, and represents a major landmark in the history of successful anticancer drugs since its clinical introduction in the 1970s [4]. Till

now, CDDP-based treatment is also the golden standard for lung cancer treatment. However, the development of chemoresistance is the main cause of treatment failure. Recent studies suggest that lncRNAs also play a significant role in chemosensitivity and some lncRNAs has been reported to be associated with CDDP resistance in lung cancer. In a study by Hou et al., lncRNA AC006050.3-003 was observed to be correlated with the response of SCC patients to CDDP-based chemotherapy. Of course, further studies are warranted to elucidate the exact molecular mechanisms by which AC006050.3-003 functions in the response of SCC cells to CDDP [69]. CITED2, a transcriptional modulator, is involved in human oncogenesis, and the lncRNA-RP11-15H7.2 has been found to be located near it. CITED2 has been reported to be involved in the resistance of cancer cells to CDDP, raising the possibility that lncRNA-RP11-15H7.2 could be a promising new therapeutic target for overcoming the developing of resistance to CDDP in lung cancer [70].

The resistance of CDDP in lung cancer cells protects the cells from the cytotoxic effects of the drugs. *p53* is a DNA-binding tumor suppressor that plays a pivotal role in DNA repair and apoptosis, and CDDP can exert its cytotoxic effect partially through regulation of the *p53* signaling pathway [71]. MEG3 activates the *p53* pathway via MDM2 suppression with consequent stimulation of GDF15 expression in turn, and finally leads to the suppression of cell proliferation. Cell cycle arrest is a critical process for DNA repair in CDDP-treated tumor cells, and therefore its failure may result in CDDP resistance. In a recent research, Liu et al. has found that MEG3 expression was markedly decreased in CDDP-resistant A549/DDP cells compared with parental A549 cells and its overexpression in A549/DDP cells increased their chemosensitivity to CDDP both *in vitro* and *in vivo* by inhibiting cell proliferation and inducing apoptosis [66]. As a member of the Bcl-2 family of proteins, Bcl-xl functions as suppressing tumor apoptosis, which is also reported to play an important role in mitochondrial permeabilization-induced apoptosis particularly through the *p53*-Bcl-xl interaction [71]. In this study, MEG3 was decreased in CDDP-insensitive lung adenocarcinoma tissues while *p53* protein levels were decreased and Bcl-xl protein levels increased. These data demonstrated that MEG3 may regulate the CDDP resistance of lung adenocarcinoma cells through the control of *p53* and Bcl-xl expression. *P21* is a cyclin-dependent kinase inhibitor that is induced by *p53* upon DNA damage or *p53* overexpression, leading to inhibition of further cell proliferation by inducing cell cycle arrest at the G1 checkpoint. Low *p21* expression has been found to promote the resistance of A549/DDP cells to CDDP. Epigenetic silencing is a common mechanism to inactivate tumor suppressor genes during carcinogenesis, and *p21* could be significantly increased in NSCLC cells after EZH2-siRNA delivery [72]. EZH2 is the components of PRC2, which works in cooperation with HOTAIR and participation in the modifications of DNA-binding proteins and then regulates global gene expression [58]. Therefore, knockdown of HOTAIR might re-sensitize the responses of A549/DDP cells to CDDP both *in vitro* and *in vivo*, at least partially through the regulation of *p21* expression [73]. lncRNA AK126698 is also reported to regulate the CDDP resistance of A549 cells partially through the canonical Wnt pathway. Wnt- β -catenin pathways are precisely controlled by a number of regulators, including the naked cuticle (NKD) family. Its two vertebrate orthologs NKD1 and NKD2 have been shown to negatively regulate canonical Wnt signaling by binding to Dvl. Knockdown of lncRNA AK126698 can significantly decrease the expression NKD2, which can negatively regulate Wnt/ β -catenin signaling. Meanwhile, knockdown of AK126698 could also increase the expression of whole β -catenin and nuclear translocation of β -catenin [74].

lncRNAs related to EGFR-TKIs resistance in lung cancer

The discovery of activating mutations in *EGFR* (exons 18-21) led to subsequent development of *EGFR* tyrosine kinase inhibitors (*EGFR*-TKIs), such as gefitinib and erlotinib, revolutionizing the treatment of lung carcinogenesis [75, 76]. *EGFR*-TKIs are now recommended as first-line therapy for lung cancer patients with these mutations. Previous studies reported that the molecular mechanisms of *EGFR*-TKIs mainly includes activation of PI3K/Akt, MEK and STAT signal pathways, which promote cell proliferation and cell apoptosis

Table 1. Biological functions of lncRNAs in lung cancer

lncRNA	Functions of lncRNA	Target genes	References
HOTAIR	Promoting cell invasive and migration and inducing chemoresistance	PRC2/HOXA5/MMP-9/MMP-2/p21	[26,58,63,64,73]
HOTTIP	Promoting cell proliferation and inhibiting apoptosis	Cdc25C/ Cyclin B1/Cyclin D1	[28]
ANRIL	Promoting cell proliferation	EZH2/PLD	[29,42]
MEG3	Inhibiting cell proliferation, inducing cell apoptosis and increasing chemosensitivity	MDM2/p53	[31,65]
TUG1	Promoting cell proliferation	PRC2	[33]
MALAT-1	Promoting cell proliferation, invasive and migration, and being involved in EGFR-TKIs resistance	MMP-9/MIA2/ROBO1/GPC6/ABCA1	[39,54,82]
PANDAR	Inhibiting cell proliferation and inducing cell apoptosis	NF-YA	[41]
AK001796	Promoting cell proliferation	BIRC5/TPDF2/CDC6/CDK5RAP1/GA DD45A/CCNC	[43]
LUADT1	Promoting cell proliferation	p27	[44]
MVIH	Promoting cell proliferation	MMP-2/MMP-9	[47]
HNF1A-AS1	Promoting cell invasive and migration	Unclear	[50]
PVT1	Promoting cell invasive and migration	Unclear	[51]
CARLo-5	Promoting cell invasive and migration	Unclear	[52]
BCYRN1	Promoting cell invasive and migration	MMP-9/MMP-13	[56]
AFAP1-AS1	Promoting cell invasive and migration	AFAP1	[57]
lnc_bc060912	Inhibiting cell apoptosis	PARP1/NPM1	[68]
AK126698	Inhibiting CDDP resistance	NKD2	[74]
GAS5	Decreasing cell viability and resistance to EGFR-TKIs	IGF-1R	[85]
DLX6-AS1	Promoting cell invasive and migration	Unclear	[86]
HMLincRNA717	Being involved in tumor progression	Unclear	[87]

in NSCLC [77, 78]. Recently, more and more important regulatory functional lncRNAs are found to play critical roles in gefitinib-resistant lung cancer cells through regulation of cell proliferation and apoptosis.

EMT is a process where epithelial cells lose their cell polarity and cell-cell adhesion, and consequently with gaining migratory and invasive properties to become mesenchymal cells [79]. Increasing evidence show that EMT is associated with the resistance of lung cancer cells to EGFR-TKIs *in vitro* [80]. Recently, some lncRNAs have been reported to promote EGFR-TKIs resistance of lung cancer by regulating EMT process. As a member of the FOX transcription factor family, FOXC1 is important in cancer development and induces EMT via inhibiting E-cadherin expression and promotes cell migration and invasion [81]. lncRNAs BC087858 is an intergenic lncRNAs, which locates near forkhead box protein C1 (FOXC1). Thus, BC087858 may induce EGFR-TKIs resistance through EMT [78]. In addition, MALAT-1 is observed be downregulated in gefitinib-resistant lung cells. MALAT-1 is linked to EMT-associated transcription factors ZEB1, ZEB2, slug and E-cadherin, but whether MALAT-1 regulates EMT to affect the sensitivity of lung cancer cells to EGFR-TKIs is still unclear. Therefore, future studies are needed to fully elucidate the possible mechanisms of MALAT-1 involved in the development of EGFR-TKIs resistance [82].

Insulin-like growth factor 1 is an important growth regulatory pathway, significantly responsible for cancer cell proliferation, migration, and apoptosis [83]. Inhibition of IGF signaling, however, seems responsible for blocking the growth and survival of tumour cells where the PI3K-AKT or ERK pathways are activated by the loss of functional PTEN or RAS-RAF activation, respectively [84]. IGF-1 signaling is regulated by insulin-like growth factor 1 receptor (IGF-1R). IGF-1R has been identified as a downstream target of GAS5, and upregulation of GAS5 can decrease cell viability and reverse EGFR-TKIs resistance of lung cancer cells by directly downregulating IGF-1R expression [85].

Discussion

Since lncRNAs receive more and more attention, increasing numbers of lncRNAs associated with lung cancer have been identified. lncRNAs preferentially express in

specific tissues and are related to differentiation status, lymph node metastases and TNM stage of patients. For example, high DLX6-AS1 expression level was closely correlated with both histological differentiation and TNM stage in lung adenocarcinoma [86]. Meanwhile, downregulation of HMLincRNA717 is reported to be involved in NSCLC progression [87]. These traits highlight the potential capability of lncRNAs to be an independent diagnostic or prognostic factor for lung cancer patients. Given the potential roles of lncRNAs in tumorigenesis, researchers have sought to identify lncRNAs which can be used for preventing or treating human cancers. Gutschner et al. reported that antisense oligonucleotides (ASO) -mediated blocking of MALAT1 could prevent the metastasis formation after tumor implantation [88]. Meanwhile, targeting p53/TUG1/PRC2/HOXB7 or p53/PANDAR/NF- κ B/Bcl-2 signaling axis may be a promising strategy for the treatment of NSCLC [33, 41]. These experimental data uncover that lncRNAs may serve as both predictive markers and therapeutic targets in lung cancer. The development of drug resistance remains as a major challenge in the treatment of lung cancer. Increasing evidence has pointed to the direct involvement of lncRNAs in the resistance of lung cancer to therapies (Table 1), suggesting that target lncRNAs may be a potential strategy for reversing the resistance of lung cancer cells to chemotherapy and molecular-targeted therapy.

Conclusions and Future Directions

In conclusion, lncRNAs can serve as diagnostic or prognostic factors in lung cancer, while they are also such compelling molecular entities with the potential to offer a new approach to overcome the development of resistance in lung cancer treatment. However, the molecular mechanisms underlying the functions of lncRNAs are not yet fully understood, and the fundamental understanding of lncRNAs remains to be extended. Based on a deeper understanding of lncRNA biology in lung cancer, the lncRNA-based therapies in the form of ASOs as well as other technologies hold great promise for overcoming chemoresistance and developing more effective personalized anticancer treatment strategies in lung cancer patients. Before lncRNA-based therapies can become a successful method for the treatment of lung cancer patients, therapeutic delivery of target lncRNAs into tumor cells or tissues and evaluation of their safety still remain major challenges.

Acknowledgements

The work was supported by grants from the National Natural Science Foundation of China (No.81172335 and 81472266) and the Excellent Youth Foundation of Jiangsu Province, China (BK20140032).

Disclosure Statement

None.

References

- 1 Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F: Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015;136:E359-386.
- 2 Lam WK, White NW, Chan-Yeung MM: Lung cancer epidemiology and risk factors in Asia and Africa. *Int J Tuberc Lung Dis* 2004;8:1045-1057.

- 3 Chheang S, Brown K: Lung cancer staging: clinical and radiologic perspectives. *Semin Intervent Radiol* 2013;30:99-113.
- 4 Ramalingam SS, Owonikoko TK, Khuri FR: Lung cancer: New biological insights and recent therapeutic advances. *CA Cancer J Clin* 2011;61:91-112.
- 5 Davidson MR, Gazdar AF, Clarke BE: The pivotal role of pathology in the management of lung cancer. *J Thorac Dis* 2013;5:S463-478.
- 6 Xia H, Hui KM: Mechanism of Cancer Drug Resistance and the involvement of noncoding RNAs. *Curr Med Chem* 2014;21:3029-3041.
- 7 Kuczyński EA, Sargent DJ, Grothey A, Kerbel RS: Drug rechallenge and treatment beyond progression-implications for drug resistance. *Nat Rev Clin Oncol* 2013;10:571-587.
- 8 Zheng Y, Wang R, Song HZ, Pan BZ, Zhang YW, Chen LB: Epigenetic downregulation of RUNX3 by DNA methylation induces docetaxel chemoresistance in human lung adenocarcinoma cells by activation of the AKT pathway. *Int J Biochem Cell Biol* 2013;45:2369-2378.
- 9 Ren J, Chen Y, Song H, Chen L, Wang R: Inhibition of ZEB1 reverses EMT and chemoresistance in docetaxel-resistant human lung adenocarcinoma cell line. *J Cell Biochem* 2013;114:1395-1403.
- 10 Wang R, Huang J, Feng B, De W, Chen L: Identification of ING4 (inhibitor of growth 4) as a modulator of docetaxel sensitivity in human lung adenocarcinoma. *Mol Med* 2012;18:874-886.
- 11 Hangauer MJ, Vaughn IW, McManus MT: Pervasive transcription of the human genome produces thousands of previously unidentified long intergenic noncoding RNAs. *PLoS Genet* 2013;9:e1003569.
- 12 Cui SY, Huang JY, Chen YT, Song HZ, Feng B, Huang GC, Wang R, Chen LB, De W: Let-7c governs the acquisition of chemo- or radioresistance and epithelial-to-mesenchymal transition phenotypes in docetaxel-resistant lung adenocarcinoma. *Mol Cancer Res* 2013;11:699-713.
- 13 Wang H, Zhu LJ, Yang YC, Wang ZX, Wang R: MiR-224 promotes the chemoresistance of human lung adenocarcinoma cells to cisplatin via regulating G(1)/S transition and apoptosis by targeting p21(WAF1/CIP1). *Br J Cancer* 2014;111:339-354.
- 14 Bar J, Gorn-Hondermann I, Moretto P, Perkins TJ, Niknejad N, Stewart DJ, Goss GD1, Dimitroulakos J4: miR Profiling Identifies Cyclin-Dependent Kinase 6 Downregulation as a Potential Mechanism of Acquired Cisplatin Resistance in Non-Small-Cell Lung Carcinoma. *Clin Lung Cancer* 2015;16:e121-129.
- 15 Wang R, Chen DQ, Huang JY, Zhang K, Feng B, Pan BZ, Chen J, De W, Chen LB: Acquisition of radioresistance in docetaxel-resistant human lung adenocarcinoma cells is linked with dysregulation of miR-451/c-Myc-survivin/rad-51 signaling. *Oncotarget* 2014;5:6113-6129.
- 16 Huang JY, Cui SY, Chen YT, Song HZ, Huang GC, Feng B, Sun M, De W, Wang R, Chen LB: MicroRNA-650 was a prognostic factor in human lung adenocarcinoma and confers the docetaxel chemoresistance of lung adenocarcinoma cells via regulating Bcl-2/Bax expression. *PLoS One* 2013;8:e72615.
- 17 Yu H, Xu Q, Liu F, Ye X, Wang J, Meng X: Identification and Validation of Long Noncoding RNA Biomarkers in Human Non-Small-Cell Lung Carcinomas. *J Thorac Oncol* 2015;10:645-654.
- 18 Wang Y, Qian CY, Li XP, Zhang Y, He H, Wang J, Chen J, Cui JJ, Liu R, Zhou H, Xiao L, Xu XJ, Zheng Y, Fu YL, Chen ZY, Chen X, Zhang W, Ye CC, Zhou HH, Yin JY, Liu ZQ: Genome-scale long noncoding RNA expression pattern in squamous cell lung cancer. *Sci Rep* 2015;5:11671.
- 19 Gibb EA, Brown CJ, Lam WL: The functional role of long non-coding RNA in human carcinomas. *Mol Cancer* 2011;10:38.
- 20 Derrien T, Johnson R, Bussotti G, Tanzer A, Djebali S, Tilgner H, Guernec G, Martin D, Merkel A, Knowles DG, Lagarde J, Veeravalli L, Ruan X, Ruan Y, Lassmann T, Carninci P, Brown JB, Lipovich L, Gonzalez JM, Thomas M, Davis CA, Shiekhattar R, Gingeras TR, Hubbard TJ, Notredame C, Harrow J, Guigó R: The GENCODE v7 catalog of human long noncoding RNAs: analysis of their gene structure, evolution, and expression. *Genome Res* 2012;22:1775-1789.
- 21 Wang Y, Gao S, Liu G, Jia R, Fan D, Feng X: Microarray expression profile analysis of long non-coding RNAs in human gastric cardiac adenocarcinoma. *Cell Physiol Biochem* 2014;33:1225-1238.
- 22 Chen J, Lin C, Yong W, Ye Y, Huang Z: Calycosin and genistein induce apoptosis by inactivation of HOTAIR/p-Akt signaling pathway in human breast cancer MCF-7 cells. *Cell Physiol Biochem* 2015;35:722-728.
- 23 Li C, Chen J, Zhang K, Feng B, Wang R, Chen L: Progress and Prospects of Long Noncoding RNAs (lncRNAs) in Hepatocellular Carcinoma. *Cell Physiol Biochem* 2015;36:423-434.

- 24 Meseure D, Drak Alsibai K, Nicolas A, Bieche I, Morillon A: Long Noncoding RNAs as New Architects in Cancer Epigenetics, Prognostic Biomarkers, and Potential Therapeutic Targets. *Biomed Res Int* 2015;2015:320214.
- 25 Wu T, Yin X, Zhou Y, Wang Z, Shen S, Qiu Y, Sun R, Zhao Z: Roles of noncoding RNAs in metastasis of nonsmall cell lung cancer: A mini review. *J Cancer Res Ther* 2015;11:c7-c10.
- 26 Loewen G, Jayawickramarajah J, Zhuo Y, Shan B: Functions of lncRNA HOTAIR in lung cancer. *J Hematol Oncol* 2014;7:90.
- 27 Zhang J, Zhang B, Wang T, Wang H: lncRNA MALAT1 overexpression is an unfavorable prognostic factor in human cancer: evidence from a meta-analysis. *Int J Clin Exp Med* 2015;8:5499-5505.
- 28 Deng HP, Chen L, Fan T, Zhang B, Xu Y, Geng Q: Long non-coding RNA HOTTIP promotes tumor growth and inhibits cell apoptosis in lung cancer. *Cell Mol Biol (Noisy-le-grand)* 2015;61:34-40.
- 29 Nie Fq, Sun M, Yang Js, Xie M, Xu Tp, Xia R, Liu YW, Liu XH, Zhang EB, Lu KH, Shu YQ: Long Noncoding RNA ANRIL Promotes Non-Small Cell Lung Cancer Cell Proliferation and Inhibits Apoptosis by Silencing KLF2 and P21 Expression. *Mol Cancer Ther* 2014;14:268-277.
- 30 Yang ZT, Li Z, Wang XG, Tan T, Yi F, Zhu H, Zhao JP, Zhou XF: Overexpression of Long Non-Coding RNA ZXF2 Promotes Lung Adenocarcinoma Progression Through c-Myc Pathway. *Cell Physiol Biochem* 2015;35:2360-2370.
- 31 Lu KH, Li W, Liu XH, Sun M, Zhang ML, Wu WQ, Xie WP, Hou YY: Long non-coding RNA MEG3 inhibits NSCLC cells proliferation and induces apoptosis by affecting p53 expression. *BMC Cancer* 2013;13:461.
- 32 Pickard MR, Mourtada-Maarabouni M, Williams GT: Long non-coding RNA GAS5 regulates apoptosis in prostate cancer cell lines. *Biochim Biophys Acta* 2013;1832:1613-1623.
- 33 Zhang EB, Yin DD, Sun M, Kong R, Liu XH, You LH, Han L, Xia R, Wang KM, Yang JS, De W, Shu YQ, Wang ZX: P53-regulated long non-coding RNA TUG1 affects cell proliferation in human non-small cell lung cancer, partly through epigenetically regulating HOXB7 expression. *Cell Death Dis* 2014;5:e1243.
- 34 Sang H, Liu H, Xiong P, Zhu M: Long non-coding RNA functions in lung cancer. *Tumour Biol* 2015;36:4027-4037.
- 35 Spizzo R, Almeida MI, Colombatti A, Calin GA: Long non-coding RNAs and cancer: a new frontier of translational research? *Oncogene* 2012;31:4577-4587.
- 36 Li CH, Chen Y: Targeting long non-coding RNAs in cancers: progress and prospects. *Int J Biochem Cell Biol* 2013;45:1895-1910.
- 37 Zhou M, Guo M, He D, Wang X, Cui Y, Yang H, Hao D, Sun J: A potential signature of eight long non-coding RNAs predicts survival in patients with non-small cell lung cancer. *J Transl Med* 2015;13:231.
- 38 Li M, Qiu M, Xu Y, Mao Q, Wang J, Dong G, Xia W1,2, Yin R5, Xu L6: Differentially expressed protein-coding genes and long noncoding RNA in early-stage lung cancer. *Tumour Biol* 2015;36:9969-9978.
- 39 Schmidt LH, Spieker T, Koschmieder S, Schäffers S, Humberg J, Jungen D, Bulk E, Hascher A, Wittmer D, Marra A, Hillejan L, Wiebe K, Berdel WE, Wiewrodt R, Muller-Tidow C: The long noncoding MALAT-1 RNA indicates a poor prognosis in non-small cell lung cancer and induces migration and tumor growth. *J Thorac Oncol* 2011;6:1984-1992.
- 40 Prensner JR, Chinnaiyan AM: The emergence of lncRNAs in cancer biology. *Cancer Discov* 2011;1:391-407.
- 41 Han L, Zhang EB, Yin DD, Kong R, Xu TP, Chen WM, Xia R, Shu YQ, De W: Low expression of long noncoding RNA PANDAR predicts a poor prognosis of non-small cell lung cancer and affects cell apoptosis by regulating Bcl-2. *Cell Death Dis* 2015;6:e1665.
- 42 Kang YH, Kim D, Jin EJ: Down-regulation of Phospholipase D Stimulates Death of Lung Cancer Cells Involving Up-regulation of the Long ncRNA ANRIL. *Anticancer Res* 2015;35:2795-2803.
- 43 Yang Q, Xu E, Dai J, Liu B, Han Z, Wu J, Zhang S, Peng B, Zhang Y, Jiang Y: A novel long noncoding RNA AK001796 acts as an oncogene and is involved in cell growth inhibition by resveratrol in lung cancer. *Toxicol Appl Pharmacol* 2015;285:79-88.
- 44 Qiu M, Xu Y, Wang J, Zhang E, Sun M, Zheng Y, Li M, Xia W, Feng D, Yin R, Xu L: A novel lncRNA, LUADT1, promotes lung adenocarcinoma proliferation via the epigenetic suppression of p27. *Cell Death Dis* 2015;6:e1858.
- 45 Shen J, Yin JY, Li XP, Liu ZQ, Wang Y, Chen J, Qu J, Xu XJ, McLeod HL, He YJ, Xia K, Jia YW, Zhou HH: The Prognostic Value of Altered eIF3a and Its Association with p27 in Non-Small Cell Lung Cancers. *PLoS One* 2014;9:e96008.

- 46 White NM, Cabanski CR, Silva-Fisher JM, Dang HX, Govindan R, Maher CA: Transcriptome sequencing reveals altered long intergenic non-coding RNAs in lung cancer. *Genome Biol* 2014;15:429.
- 47 Nie FQ, Zhu Q, Xu TP, Zou YF, Xie M, Sun M, Xia R, Lu KH: Long non-coding RNA MVIH indicates a poor prognosis for non-small cell lung cancer and promotes cell proliferation and invasion. *Tumour Biol* 2014;35:7587-7594.
- 48 Qiu M, Xu Y, Yang X, Wang J, Hu J, Xu L, Yin R: CCAT2 is a lung adenocarcinoma-specific long non-coding RNA and promotes invasion of non-small cell lung cancer. *Tumour Biol* 2014;35:5375-5380.
- 49 Zhang E, Li W, Yin D, De W, Sun S, Han L: c-Myc-regulated long non-coding RNA H19 indicates a poor prognosis and affects cell proliferation in non-small-cell lung cancer. *Tumour Biol* 2016;37:4007-4015.
- 50 Yang X, Song JH, Cheng Y, Wu W, Bhagat T, Yu Y, Abraham JM, Ibrahim S, Ravich W, Roland BC, Khashab M, Singh VK, Shin EJ, Yang X, Verma AK, Meltzer SJ, Mori Y: Long non-coding RNA HNF1A-AS1 regulates proliferation and migration in oesophageal adenocarcinoma cells. *Gut* 2014;63:881-890.
- 51 Yang YR, Zang SZ, Zhong CL, Li YX, Zhao SS, Feng XJ: Increased expression of the lncRNA PVT1 promotes tumorigenesis in non-small cell lung cancer. *Int J Clin Exp Pathol* 2014;7:6929-6935.
- 52 Luo J, Tang L, Zhang J, Ni J, Zhang HP, Zhang L, Xu JF, Zheng D: Long non-coding RNA CARLo-5 is a negative prognostic factor and exhibits tumor pro-oncogenic activity in non-small cell lung cancer. *Tumour Biol* 2014;35:11541-11549.
- 53 Zhang J, Zhu N, Chen X: A novel long noncoding RNA LINC01133 is upregulated in lung squamous cell cancer and predicts survival. *Tumour Biol* 2015;36:7465-7471.
- 54 Zhu L, Liu J, Ma S, Zhang S: Long Noncoding RNA MALAT-1 Can Predict Metastasis and a Poor Prognosis: a Meta-Analysis. *Pathol Oncol Res* 2015;21:1259-1264.
- 55 Spector DL, Lamond AI: Nuclear Speckles. *Cold Spring Harb Perspect Biol* 2010;3:a000646-a000646.
- 56 Hu T, Lu YR: BCYRN1, a c-MYC-activated long non-coding RNA, regulates cell metastasis of non-small-cell lung cancer. *Cancer Cell Int* 2015;15:36.
- 57 Zeng Z, Bo H, Gong Z, Lian Y, Li X, Li X, Zhang W, Deng H, Zhou M, Peng S, Li G, Xiong W: AFAP1-AS1, a long noncoding RNA upregulated in lung cancer and promotes invasion and metastasis. *Tumour Biol* 2016;37:729-737.
- 58 Ono H, Motoi N, Nagano H, Miyauchi E, Ushijima M, Matsuura M, Okumura S, Nishio M, Hirose T, Inase N, Ishikawa Y: Long noncoding RNA HOTAIR is relevant to cellular proliferation, invasiveness, and clinical relapse in small-cell lung cancer. *Cancer Med* 2014;3:632-642.
- 59 Nakagawa T, Endo H, Yokoyama M, Abe J, Tamai K, Tanaka N, Sato I, Takahashi S, Kondo T, Satoh K: Large noncoding RNA HOTAIR enhances aggressive biological behavior and is associated with short disease-free survival in human non-small cell lung cancer. *Biochem Biophys Res Commun* 2013;436:319-324.
- 60 Zhuang Y, Wang X, Nguyen HT, Zhuo Y, Cui X, Fewell C, Flemington EK, Shan B: Induction of long intergenic non-coding RNA HOTAIR in lung cancer cells by type I collagen. *J Hematol Oncol* 2013;6:35.
- 61 Gloss BS, Dinger ME: The specificity of long noncoding RNA expression. *Biochim Biophys Acta* 2016;1859:16-22.
- 62 Zhou C, Ye L, Jiang C, Bai J, Chi Y, Zhang H: Long noncoding RNA HOTAIR, a hypoxia-inducible factor-1 α activated driver of malignancy, enhances hypoxic cancer cell proliferation, migration, and invasion in non-small cell lung cancer. *Tumor Biology* 2015;36:9179-9188.
- 63 Liu XH, Liu ZL, Sun M, Liu J, Wang ZX, De W: The long non-coding RNA HOTAIR indicates a poor prognosis and promotes metastasis in non-small cell lung cancer. *BMC Cancer* 2013;13:464.
- 64 Zhao W, An Y, Liang Y, Xie XW: Role of HOTAIR long noncoding RNA in metastatic progression of lung cancer. *Eur Rev Med Pharmacol Sci* 2014;18:1930-1936.
- 65 Benetatos L, Vartholomatos G, Hatzimichael E: MEG3 imprinted gene contribution in tumorigenesis. *Int J Cancer* 2011;129:773-779.
- 66 Liu J, Wan L, Lu K, Sun M, Pan X, Zhang P, Lu B, Liu G, Wang Z: The Long Noncoding RNA MEG3 Contributes to Cisplatin Resistance of Human Lung Adenocarcinoma. *PLoS One* 2015;10:e0114586.
- 67 Zhao XY, Lin JD: Long Noncoding RNAs: A New Regulatory Code in Metabolic Control. *Trends Biochem Sci* 2015;40:586-596.
- 68 Luo H, Sun Y, Wei G, Luo J, Yang X, Liu W, Guo M, Chen R: Functional Characterization of Long Noncoding RNA Lnc_bc060912 in Human Lung Carcinoma Cells. *Biochemistry* 2015;54:2895-2902.

- 69 Hou Z, Xu C, Xie H, Xu H, Zhan P, Yu L, Fang X: Long noncoding RNAs expression patterns associated with chemo response to cisplatin based chemotherapy in lung squamous cell carcinoma patients. *PLoS One* 2014;9:e108133.
- 70 Wang Y, Chen W, Yang C, Wu W, Wu S, Qin X, Li X: Long non-coding RNA UCA1a(CUDR) promotes proliferation and tumorigenesis of bladder cancer. *Int J Oncol* 2012;41:276-284.
- 71 Wang S, Li W, Xue Z, Lu Y, Narsinh K, Fan W, Li X, Bu Q, Wang F, Liang J, Wu K, Cao F: Molecular imaging of p53 signal pathway in lung cancer cell cycle arrest induced by cisplatin. *Mol Carcinog* 2013;52:900-907.
- 72 Cao W, Ribeiro Rde O, Liu D, Saintigny P, Xia R, Xue Y, Lin R, Mao L, Ren H: EZH2 promotes malignant behaviors via cell cycle dysregulation and its mRNA level associates with prognosis of patient with non-small cell lung cancer. *PLoS One* 2012;7:e52984.
- 73 Liu Z, Sun M, Lu K, Liu J, Zhang M, Wu W, De W, Wang Z, Wang R: The long noncoding RNA HOTAIR contributes to cisplatin resistance of human lung adenocarcinoma cells via downregulation of p21(WAF1/CIP1) expression. *PLoS One* 2013;8:e77293.
- 74 Yang Y, Li H, Hou S, Hu B, Liu J, Wang J: The noncoding RNA expression profile and the effect of lncRNA AK126698 on cisplatin resistance in non-small-cell lung cancer cell. *PLoS One* 2013;8:e65309.
- 75 Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, Sunpaweravong P, Han B, Margono B, Ichinose Y, Nishiwaki Y, Ohe Y, Yang JJ, Chewaskulyong B, Jiang H, Duffield EL, Watkins CL, Armour AA, Fukuoka M: Gefitinib or Carboplatin–Paclitaxel in Pulmonary Adenocarcinoma. *N Engl J Med* 2009;361:947-957.
- 76 Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, Gemma A, Harada M, Yoshizawa H, Kinoshita I, Fujita Y, Okinaga S, Hirano H, Yoshimori K, Harada T, Ogura T, Ando M, Miyazawa H, Tanaka T, Saijo Y, Hagiwara K, Morita S, Nukiwa T; North-East Japan Study Group: Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med* 2010;362:2380-2388.
- 77 Li H, Schmid-Bindert G, Wang D, Zhao Y, Yang X, Su B, Zhou C: Blocking the PI3K/AKT and MEK/ERK signaling pathways can overcome gefitinib-resistance in non-small cell lung cancer cell lines. *Adv Med Sci* 2011;56:275-284.
- 78 Sordella R1, Bell DW, Haber DA, Settleman J: Gefitinib-sensitizing EGFR mutations in lung cancer activate anti-apoptotic pathways. *Science* 2004;305:1163-1167.
- 79 Xia L, Huang W, Tian D, Zhu H, Qi X, Chen Z, Zhang Y, Hu H, Fan D, Nie Y, Wu K: Overexpression of forkhead box C1 promotes tumor metastasis and indicates poor prognosis in hepatocellular carcinoma. *Hepatology* 2013;57:610-624.
- 80 Uramoto H, Iwata T, Onitsuka T, Shimokawa H, Hanagiri T, Oyama T: Epithelial–Mesenchymal Transition in EGFR-TKI Acquired Resistant Lung Adenocarcinoma. *Anticancer Res* 2010;30:2513-2517.
- 81 Iwatsuki M, Mimori K, Yokobori T, Ishi H, Beppu T, Nakamori S, Baba H, Mori M: Epithelial-mesenchymal transition in cancer development and its clinical significance. *Cancer Sci* 2010;101:293-299.
- 82 Cheng N, Li X, Zhao C, Ren S, Chen X, Cai W, Zhao M, Zhang Y, Li J, Wang Q, Zhou C: Microarray expression profile of long non-coding RNAs in EGFR-TKIs resistance of human non-small cell lung cancer. *Oncol Rep* 2015;33:833-839.
- 83 Reinmuth N, Kloos S, Warth A, Risch A, Muley T, Hoffmann H, Thomas M, Meister M: Insulin-like growth factor 1 pathway mutations and protein expression in resected non-small cell lung cancer. *Hum Pathol* 2014;45:1162-1168.
- 84 Agulló-Ortuño MT1, Díaz-García CV, Agudo-López A, Pérez C, Cortijo A, Paz-Ares L, López-Ríos F, Pozo F, de Castro J, Cortés-Funes H, López Martín JA: Relevance of insulin-like growth factor 1 receptor gene expression as a prognostic factor in non-small-cell lung cancer. *J Cancer Res Clin Oncol* 2015;141:43-53.
- 85 Dong S, Qu X, Li W, Zhong X, Li P, Yang S, Chen X, Shao M, Zhang L: The long non-coding RNA, GAS5, enhances gefitinib-induced cell death in innate EGFR tyrosine kinase inhibitor-resistant lung adenocarcinoma cells with wide-type EGFR via downregulation of the IGF-1R expression. *J Hematol Oncol* 2015;8:43.
- 86 Li J, Li P, Zhao W, Yang R, Chen S, Bai Y, Dun S, Chen X, Du Y, Wang Y, Zang W, Zhao G, Zhang G: Expression of long non-coding RNA DLX6-AS1 in lung adenocarcinoma. *Cancer Cell Int* 2015;15:48.
- 87 Xie X, Liu HT, Mei J, Ding FB, Xiao HB, Hu FQ, Hu R, Wang MS: LncRNA HMLincRNA717 is down-regulated in non-small cell lung cancer and associated with poor prognosis. *Int J Clin Exp Pathol* 2014;7:8881-8886.
- 88 Gutschner T, Hämmerle M, Diederichs S: MALAT1 - a paradigm for long noncoding RNA function in cancer. *J Mol Med (Berl)* 2013;91:791-801.