Role of long non-coding RNA in drug resistance in non-small cell lung cancer

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Abstract
Lung cancer is the leading cause of cancer-associated death, and non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancer cases. Many drugs have been used to treat NSCLC in order to improve patient prognosis. Platinum-based chemotherapy is the first-line treatment for locally advanced or metastatic patients. For patients with activating EGFR mutations, tyrosine kinase inhibitors are the best treatment choice. NSCLC initially exhibits an excellent response to treatment; however, acquired resistance has been observed in many patients, leading to ineffective treatment. Clinical resistance is an impediment in the treatment of patients with advanced NSCLC. Many sequencing technologies have shown that long non-coding RNA (lncRNA) is expressed differently between drug-resistant and drug-sensitive lung cancer cells. We review the literature on lncRNA in drug resistance of NSCLC. The aim of this review is to gain insight into the molecular mechanisms of drug resistance, mainly focusing on the role of lncRNA in NSCLC.

Introduction
Lung cancer is the leading cause of cancer death worldwide as a result of high incidence and mortality.1 Lung cancer is traditionally classified as small cell lung cancer (SCLC) and non-small lung cancer (NSCLC).2–4 NSCLC accounts for 85% of lung cancer cases.5 NSCLC patient prognosis is poor as nearly half present with metastatic disease at diagnosis.6 Platinum-based combination chemotherapy is currently recommended as a standard treatment for patients with advanced NSCLC.

Cisplatin (DDP) remains the most widely employed first-line chemotherapeutic agent for the treatment of lung cancer.7 EGFR-directed therapies have now emerged as the best option for NSCLC patients with an EGFR mutation in exons 19 or 21.8 However, individuals respond to drug therapy differently and the efficacy of drug treatment is often impaired after the emergence of drug resistance. Clinical resistance is considered an impediment to the treatment of patients with advanced NSCLC, and can be affected by many factors.9 In addition to patients failing to receive...
standardized treatment on time, factors such as the abnormal regulation of molecular levels, including DNA damage repair, regulation of signaling pathways, and epithelial-to-mesenchymal transition (EMT), can contribute to drug resistance. Investigating the mechanisms of drug resistance and identifying strategies to overcome such resistance are thus important clinical goals.

Long non-coding RNAs (lncRNAs) and non-small cell lung cancer (NSCLC)

The human transcription comprises a large number of protein-coding messenger RNAs (mRNAs), and a large set of non-protein coding RNAs (ncRNAs). With the help of advanced techniques, scientists have determined that 87.3% of the human genome is actively transcribed, although < 3% of the total human sequence encodes proteins. These discoveries revealed widespread expression of ncRNA. NcRNA can further be divided into two classes: small ncRNAs with a length of < 200 bps and long ncRNAs (lncRNA) with a length > 200 bps.

LncRNAs are non-protein coding transcripts and play an important regulatory role in cancer development, metastasis, and prognosis. Various studies have suggested that the dysregulation of lncRNA is associated with lung cancer. Compared to normal lung tissue, lnc01433 is significantly overexpressed and promotes migration and invasion in NSCLC. LINC00094 is highly expressed in lung cancer tissues and could be a molecular target for therapy for smoking-related lung cancer. In recent years, emerging evidence has confirmed the role of lncRNAs in drug resistance.

The many lncRNAs associated with lung cancer are listed in Table 1. However, the mechanism by which changes in lncRNA levels affect the expression of gene products that may contribute to drug resistance remains largely unknown. Drug resistance poses a great challenge to clinical treatment; therefore, the relationship between lncRNAs and drug resistance has attracted much attention. Herein, we review the literature on lncRNA in drug resistance of NSCLC. We focus on the roles of lncRNA in DDP resistant NSCLC and EGFR-tyrosine kinase inhibitor (TKI) resistant NSCLC.

| LncRNA | Key factors | Functions | Reference |
|--------|-------------|-----------|-----------|
| linc01433 | Promotes migration and invasion | 13 |
| LINC00094 | Highly expressed in lung cancer tissues | 14 |
| Trp53corl | cdkn1a | DDP resistance | 26 |
| DOSR1 | BRCA1, hnrNPU1 | DDP resistance | 27 |
| HOTAIR | p21, EZH2 | DDP resistance, poor prognosis, advanced stage, shorter disease-free survival | 28 |
| TRPM2-AS | P66hc | DDP resistance | 29 |
| ROR | | DDP resistance | 30 |
| HI9 | FAS, BAX, BAK | DDP resistance, suppresses apoptosis, promotes cell growth | 31 |
| MEG3 | | DDP resistance, suppresses cell apoptosis, induces apoptosis | 32–35 |
| SNHG12 | MAPK1, MAP2K1 | DDP resistance | 37 |
| NEAT1 | CTR1 | DDP resistance | 38 |
| AK126698 | NKD | DDP resistance | 40–42 |
| RP11-15H7.2 | CITED2 | DDP resistance | 43 |
| BC087858 | FOXC1 | EGFR-TKI resistance | 59,60 |
| MALAT1 | ZEB1, ZEB2, slug, E-cadherin | EGFR-TKI resistance, poor prognosis, shorter overall survival, metastasis survival | 61–64 |
| MIR31HG | | EGFR-TKI resistance | 70 |
| UCA1 | E-cadherin, vimentin, snail, N-cadherin | EGFR-TKI and DDP resistance | 67,72 |
| GASS | IGF-1R | EGFR-TKI resistance, induces apoptosis | 73 |

DDP, cisplatin; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

LncRNAs and cisplatin (DDP) resistance

Combination chemotherapy based on platinum is a standard adjunctive treatment strategy for advanced NSCLC following surgical resection. DDP is the most commonly used platinum drug that inhibits DNA replication and destroys cell membrane structure. However, DDP resistance is the primary cause of chemotherapy failure. Therefore, investigation of the molecular mechanisms underlying DDP resistance in NSCLC is of great significance for improving patient outcomes. Recent studies have reported that lncRNA plays a vital role in NSCLC and that some lncRNAs are associated with DDP resistance.

Platinum-based chemotherapy plays a key role in the treatment of NSCLC by damaging DNA and inducing tumor cell death. An increasing number of studies have proven that sensitivity to chemotherapy varies from person to person, because large interindividual variability exists in the
capacity for DNA damage response and repair. Previous studies have indicated that NSCLC cells with different functional status of the various DNA repair pathways display different responses to DDP. A growing body of evidence indicates that enhanced DNA damage repair ability is involved in conferring DDP resistance. DNA damage response and repair capacity is closely related to sensitivity to chemotherapy (Fig 1). Directly targeting the DNA pathway involved in DDP resistance is an effective strategy to overcome such resistance in NSCLC.

With the evolution of DNA sequencing and bioinformatics, lncRNAs are emerging as a novel research field as they interact with DNA, RNA, and proteins. Recently, numerous lncRNAs were shown to correlate with drug resistance in lung cancer in a p53-dependent manner. LncRNA-p21 (Trp53cor1) affects the expression of hundreds of gene targets that are normally repressed by p53. Moreover, lncRNA-p21 knockout mice have enforced the G1/S checkpoint, which causes increased proliferation by decreasing Cdkn1a expression. LncRNA DDSR1, induced by the ataxia telangiectasia mutated (ATM)-NF-κB pathway, can increase the capacity for DNA repair by homologous recombination through interaction with BRCA1 and hnRNPU1. However, whether DDSR1 promotes DDP resistance via the DNA repair pathway requires further verification. P21, a cyclin-dependent kinase inhibitor, has the ability to inhibit cell proliferation and is induced by p53 upon DNA damage or p53 overexpression. Low p21 expression has been found to promote resistance to DDP. EZH2 is reported to participate in the modifications of DNA binding proteins, subsequently regulating global gene expression via cooperation with lncRNA HOTAIR. In conclusion, lncRNA HOTAIR contributes to DDP resistance via the downregulation of p21 expression and interaction with EZH2, which leads to chromosome modifications.

LncRNAs play critical roles in DNA repair. Differentially expressed lncRNA modulates repair capacity in NSCLC, thus presenting a novel strategy to overcome resistance. Although many studies have been carried out to identify the molecular mechanisms of drug resistance, current research regarding the roles of lncRNA regulation in the DNA repair pathway is still limited, thus further studies are urgently required.

**LncRNAs promote DDP resistance by regulating the cell signaling pathway**

In addition to regulating the ability of DNA repair to promote DDP resistance, lncRNAs can also cause resistance through many other pathways. Many studies have shown that lncRNAs can lead to drug resistance by regulating cellular signaling pathways. P66shc, a pro-oxidant protein in mitochondria, could negatively regulate lifespan. Downregulated lncRNA TRPM2-AS inhibits DDP resistance via activation of the p53-p66shc pathway in NSCLC. Silencing lncRNA ROR improves sensitivity to DDP in NSCLC by regulating the PI3K/AKT/mTOR signaling pathway. LncRNA H19 is related to apoptosis proteins FAS, BAX, and BAK, and high H19 levels are negatively associated with patient response to DDP-based chemotherapy. Therefore, H19 may be an oncogenic factor in DDP resistance of NSCLC.

MEG3, an imprinted lncRNA within the DLK1-MEG3 locus located at human chromosome 14q32, is reported to regulate DDP sensitivity through many mechanisms. Liu et al. found that MEG3 overexpression increased DDP sensitivity both in vitro and in vivo by hindering cell proliferation and promoting apoptosis. Xia et al. reported that MEG3 downregulation enhances the DDP resistance of lung cancer cells by activating the Wnt/β-catenin signaling pathway. Wang et al. proved that MEG3 enhances DDP sensitivity in NSCLC by regulating the miR-21-5p/SOX7 axis. Therefore, MEG3 may be a potential target for reversing DDP resistance in lung cancer. MEG3 acts as a competing endogenous RNA by sponging specific micro RNAs (miRNAs). Previous studies have confirmed that lncRNAs can act as miRNA sponges, reducing the regulatory effects of miRNA. LncRNA SNHG12 also acts as a competing endogenous RNA to regulate MAPK1 and MAP2K1 by sponging miR-181a in NSCLC.

![Figure 1](image-url)
LncRNA in drug resistance in NSCLC

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knockdown enhances DDP sensitivity in NSCLC in vivo. Upregulation of lncRNA NEAT1 could function as a competing endogenous lncRNA in lung cancer, mediating CTR1 by sponging miRNA-98-5p to enhance DDP sensitivity. All of these findings present new strategies to overcome chemoresistance in NSCLC.

The development of molecular biotechnologies makes it possible to detect molecular differences between different subsets of cells. Hou et al. identified 1702 lncRNAs that were differentially expressed between DDP-sensitive and DDP-resistant patients. Compared with DDP-resistant patients, lncRNA AC006050.3-003 was significantly downregulated in DDP-sensitive patients, proving that AC006050.3-003 may be a biomarker for DDP resistance. Another study confirmed that there are 1380 lncRNAs differentially expressed between A549/DDP and A549 parental cells. A gene co-expression network identified that lncRNAs, including BX648420, ENST00000366408, and AK126698, potentially play a key role in DDP resistance. AK126698, discovered by direct sequencing in 2003, is a 3820bp lncRNA in the cerebellum. The Wnt/β-catenin canonical signaling pathway was previously believed to play a central role in determining cell fate and is controlled by many regulators. The naked cuticle (NKD) family, as one of the regulators of signaling pathways, includes Drosophila NKD and its two vertebrate orthologs, N KD1 and NKD2, is reported to negatively regulate the Wnt/β-catenin canonical signaling pathway inhibited by binding to the Dvl protein. AK126698 may play an important role in NSCLC DDP resistance through the Wnt pathway. However, the exact mechanism by which AK126698 regulates the Wnt pathway requires further elucidation.

Research has also suggested that lncRNAs may lead to lung cancer resistance to drugs by regulating adjacent genes. LncRNA-RP11-15H7.2, a 1580bp intergenic lncRNA, is found to be located near CITED2, which is a transcriptional modulator involved in the resistance of cancer cells to DDP. Therefore, LncRNA-RP11-15H7.2 may influence chemoresistance by regulating neighboring genes.

LncRNAs have become a hot research topic in recent years and many experiments have been conducted to prove their relationship with DDP resistance; however, the exact mechanisms have not yet been identified. There are significant differences in microarray expression of LncRNAs between DDP-resistant and DDP-sensitive cell lines. Therefore, LncRNAs offer an opportunity to develop potential predictors for chemotherapeutic targets in NSCLC.

LncRNAs and EGFR-tyrosine kinase inhibitor (TKI) resistance

EGFR has been identified as an oncogenic driver. Blockade of EGFR with specific TKIs is the first-line treatment for advanced NSCLC. The development of EGFR-TKIs (gefitinib, erlotinib, and afatinib) is a milestone for the treatment of NSCLC harboring EGFR-activating mutations; however, to date, drug resistance still greatly limits the usefulness of anti-EGFR agents.

LncRNAs promote EGFR-TKI resistance by regulating the epithelial-to-mesenchymal transition (EMT) process

Sensitive mutation in the EGFR gene is associated with a dramatic clinical response to EGFR-TKIs in NSCLC. Despite an initial response to EGFR-TKI treatment, most patients eventually acquire drug resistance and experience disease progression. A secondary T790M mutation, MET amplification, and overexpression of hepatocyte growth factor (HGF) are well-studied mechanisms underlying acquired resistance to EGFR-TKIs. EMT also plays a part in determining the sensitivity to EGFR-TKIs. EMT is a process in which the expression of epithelial markers, such as E-cadherin and gamma catenin, is decreased, and mesenchymal markers, such as vimentin and fibronectin, is increased.

Increasing evidence shows that the mesenchymal phenotype is more resistant to EGFR-TKIs than the epithelial phenotype in vitro. For example, lung cancer cell lines undergoing EMT, with expression of vimentin and/or fibronectin, were insensitive to EGFR-TKIs. Moreover, the restoration of epithelial markers, such as E-cadherin and gamma catenin, enhances the sensitivity of cancer cells to EMT. At the same time, many lncRNAs are reported to promote EGFR-TKI resistance by regulating the EMT process.

As a member of the FOX transcription factor family, FOXC1 is important for cancer development. LncRNA-BC087858 is an intergenic lncRNA located near the FOXC1 gene. FOXC1 promotes EMT by inhibiting E-cadherin expression and inducing cell migration and invasion, suggesting that BC087858 may be associated with EGFR-TKI resistance through EMT. As the first identified lncRNA in lung cancer, MALAT1 (also known as NEAT2) is downregulated in gefitinib-resistant cells. This highly conserved lncRNA has been well studied in recent years. Its potential roles in the regulation of EMT-associated gene transcription, such as ZEB1, ZEB2, slug, and E-cadherin, have been reported. MALAT1 is linked to EMT associated transcription factors. ZEB1 is reported to mediate acquired EGFR-TKI resistance in NSCLC. Moreover, MALAT1 promotes EMT by activating the Wnt signaling pathway. The mechanism by which MALAT1 regulates EMT to affect sensitivity to EGFR-TKIs is unclear. Therefore, future studies are needed to elucidate...
the possible mechanism by which lncRNAs may promote resistance to EGFR-TKIs.

**IncRNAs promote EGFR-TKI resistance by regulating the cell signaling pathway**

Previous studies have proven that activation of the PI3K/AKT and MEK/ERK cell signaling pathways, as well as EMT, is associated with EGFR-TKI resistance in NSCLC. Blocking the PI3K/AKT and MEK/ERK pathways could restore sensitivity to gefitinib-resistant NSCLC cell lines. This evidence indicates that lncRNAs regulate the cell signaling pathway that leads to EGFR-TKI resistance.

PI3K/AKT is an important downstream mediator of the EGFR signaling cascade. Dysregulation of the PI3K/AKT signaling pathway is associated with reduced rates of apoptosis and the phenotype of multidrug resistance. Wang et al. revealed that overexpression of MIR31HG lncRNA contributes to gefitinib resistance in NSCLC cell lines, affecting cell proliferation, apoptosis, and the cell cycle by activating the EGFR/PI3K/AKT pathway.

LncRNA UCA1 was first identified in bladder cancer cells and is involved in the invasion and progression of bladder cancer. In lung cancer, overexpression of UCA1 induces non-T790M acquired resistance to EGFR-TKIs by activating the AKT/mTOR pathway. Knockdown of UCA1 enhances E-cadherin expression, but attenuates vimentin, snail, and N-cadherin expression. UCA1 is upregulated in lung cancer and induces chemoresistance. These factors suggest that lncRNA UCA1 regulates resistance to EGFR-TKIs, not only by activating the AKT/mTOR pathway but also by activating EMT. The downregulation of lncRNA GAS5 is not only related to tumorigenesis and progression, but also to EGFR-TKI resistance. Although IGF-1R has been identified as a key downstream mediator of GAS5, specific signaling pathways still need to be elucidated.

Cheng et al. found a total of 22,578 differentially expressed lncRNAs between EGFR-TKI-sensitive and EGFR-TKI-resistant human lung cancer cells by microarray. Based on analysis using the Kyoto Encyclopedia of Genes and Genomes database, the enriched pathways of these lncRNAs are associated with cell proliferation and apoptosis. Previous studies have reported that EGFR-TKI resistance is connected to cell proliferation and apoptosis. LncRNAs may, therefore, present novel candidate biomarkers for future therapeutic strategies involving EGFR-TKIs.

**Other drugs related to IncRNAs**

Besides DDP and TKIs, many other drugs are used to treat NSCLC. As time goes on, these drugs eventually become insensitive to cancer cells. Studies have shown that resistance is associated with IncRNAs. LncRNA KCNQ1OT1 expression is much higher in lung adenocarcinoma patients sensitive to paclitaxel than in those not sensitive to paclitaxel. Knockdown of KCNQ1OT1 depresses chemoresistance to paclitaxel in lung adenocarcinoma patients. In SCLC, IncRNA TUG1 is involved in chemoresistance by regulating LIMK2b via EZH2.

**Conclusion**

Previous studies have suggested that IncRNA dysregulation in NSCLC is associated with lymph node metastasis, advanced stage, metastasis development, and poor patient prognosis. Anti-tumor drug resistance in various carcinomas, including colon, bladder, ovarian, and gastric cancers, and NSCLC, is associated with IncRNAs. Although advances have been achieved in diagnosis and treatment, NSCLC is still one of the most common malignancies, with five-year survival rates < 15%. A combination of DDP-based chemotherapy and EGFR-TKIs is commonly used as a treatment regimen for advanced NSCLC patients. Drug resistance remains one of the most important predictors associated with patient prognosis. Therefore, further elucidation of the molecular mechanisms of drug resistance is required to improve outcomes for NSCLC patients.
As previously mentioned, DDP can lead to DNA damage and induce tumor cell death, and different patients exhibit different drug sensitivities and abilities to repair DNA damage. Various studies have suggested that lncRNA dysregulation is involved in DDP resistance by regulating the nearby genes, modulating repairing factors, and affecting signaling pathways. Not surprisingly, targeting lncRNAs may be a potential strategy for reversing NSCLC resistance to DDP-based chemotherapy. EMT contributes to drug resistance, rather than metastasis. LncRNAs are involved in EGFR-TKI resistance by regulating the EMT phenotype. The molecular mechanisms by which lncRNAs regulate EGFR-TKI resistance are still unknown. Furthermore, many signaling pathways could be targets of certain lncRNAs, regulating EGFR-TKI resistance.

In conclusion, research of lncRNAs and drug resistance has attracted much attention in recent years. Numerous lncRNAs have been proven to be involved in drug resistance. Further studies focusing on lncRNA function are required to improve the response to therapeutic drugs. The relationship between lncRNAs and drug resistance may serve as a new prognostic biomarker for lung cancer.

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Disclosure

No authors report any conflict of interest.

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