Emerging role of long non-coding RNAs in cisplatin resistance

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Abstract: Cisplatin (CDDP) is one of the most commonly used chemotherapy drugs for the treatment of various cancers. Although platinum-based therapies are highly efficacious against rapidly proliferating malignant tumors, the development of CDDP resistance results in significant relapse as well as decreased overall survival rates, which is a significant obstacle in CDDP-based cancer therapy. Long non-coding RNAs (lncRNAs) are involved in cancer development and progression by the regulation of processes related to chromatin remodeling, transcription, and posttranscriptional processing. Emerging evidence has recently highlighted the roles of lncRNAs in the development of CDDP resistance. In this review, we discuss the roles and mechanisms of lncRNAs in CDDP chemoresistance, including changes in cellular uptake or efflux of a drug, intracellular detoxification, DNA repair, apoptosis, autophagy, cell stemness, and the related signaling pathways, aiming to provide potential lncRNA-targeted strategies for overcoming drug resistance in cancer therapy.

Keywords: cisplatin, lncRNAs, chemoresistance, cancer

Introduction
Cancer significantly affects the quality of life and is a leading cause of death worldwide. It has been reported that about 14.1 million new cancer cases and 8.2 million deaths occurred in 2012 worldwide.1 In 2018, 1,735,350 new cancer cases and 609,640 cancer deaths are projected to occur in the USA.2 Increasing national investment in cancer research contributes to accelerating progress in the prevention and treatment of cancer. Currently, the gold standard for antitumor therapeutic strategies is a combination of chemotherapy and surgery. However, chemotherapeutic anticancer agents are the standard treatment regimen for patients in whom surgery is not a viable option.3 Cisplatin is one of the most widely used and successful cytotoxic drugs for the treatment of a broad variety of tumors such as ovarian, testicular, bladder, lung, esophageal, and nasopharyngeal carcinoma (NPC). Since the discovery of the antitumor activity of cisplatin, novel platinum-based agents (carboplatin and oxaliplatin) have been developed with reduced side effects and increased efficacy.4 However, as a prototype of platinum-based agent, cisplatin remains widely used as a chemotherapeutic agent. When cisplatin is used in platinum-based chemotherapy, nearly 85% of patients with metastatic testicular cancer can be cured5 and the 5-year survival rate in patients with completely resected non-small-cell lung cancer (NSCLC) tumors is improved.6 Nevertheless, there exist many patients intrinsically resistant to cisplatin-based therapies, especially with colorectal, lung, and prostate cancers. What is more, originally sensitive tumors eventually develop chemoresistance, which is frequently observed in ovarian cancer.7 Chemoresistance allows the cancer cells to become increasingly antagonistic and improves the ability of cancer invasion and migration, leading to tumor relapse.
and poor prognosis.\textsuperscript{8,9} Emerging studies have revealed that dysregulated expression of long non-coding RNAs (lncRNAs) plays an essential role in cisplatin resistance.\textsuperscript{10} The lncRNAs, which are $>200$ nucleotides (nt) in length and which lack a significant open reading frame, may play major roles in a wide variety of biological pathways and cellular processes at the epigenetic, transcriptional, and posttranscriptional levels.\textsuperscript{10,11}

Here, we briefly review the functions and mechanisms of lncRNAs in the regulation of drug resistance in cancer cells, mainly focusing on cisplatin chemoresistance.

\textbf{Cisplatin}

As an alkylating agent, cisplatin was first described by Michele Peyrone in 1845, and its antitumor activity was discovered in the 1970s.\textsuperscript{12,13} Since its approval by the US Food and Drug Administration for the treatment of testicular and ovarian cancer in 1987,\textsuperscript{12,14} cisplatin has gradually become a first-line chemotherapeutic agent. The platinum atom of cisplatin interacts with nucleophilic N\textsuperscript{7}-sites of purine in DNA to form inter- and intra-strand DNA crosslinks,\textsuperscript{8,14} which results in DNA damage, cell cycle arrest, and activation of multiple signal transduction pathways, leading to cell apoptosis.\textsuperscript{8,15} Moreover, cisplatin-induced production of reactive oxygen species and activation of inflammatory pathways may also contribute to the induction of apoptosis.\textsuperscript{16} The introduction of cisplatin for the treatment of testicular cancer has improved its cure rate from 10\% to 85\%.\textsuperscript{17} Unfortunately, the development of cisplatin resistance limits its efficacy in cancer treatment. Studies over the years have revealed multiple potential mechanisms related to cisplatin resistance (Figure 1). Cisplatin resistance may occur through reduced intracellular platinum accumulation due to decreased drug uptake or increased drug export in cancer cells. Downregulation of copper transporter 1 (CTR1) has been associated with resistance to cisplatin by reducing cisplatin uptake.\textsuperscript{18} On the other hand, the efflux of cisplatin is mediated by transporting P-type adenosine triphosphatases (ATP) 7A and ATP7B, or multidrug-resistance-associated proteins (MRPs) in the cell membrane, and an upregulation of these efflux transporters is one of the major mechanisms of cisplatin resistance.\textsuperscript{19} Cisplatin scavenging by intracellular detoxification is another major mechanism of cisplatin resistance, in which glutathione (GSH) plays a key role in the overexpression of enzymes involved in GSH synthesis and GSH conjugation has been reported to be associated with cisplatin resistance.\textsuperscript{20} In addition, activation of the DNA damage systems, such as the nucleotide excision repair system, can attenuate the apoptotic process, leading

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig1.png}
\caption{Molecular mechanisms of cisplatin resistance.}
\textbf{Notes:} Multiple cellular alterations in cancer cells, including cell cycle, apoptosis, autophagy, stemness, intracellular detoxification, and drug influx/efflux, contribute to cisplatin chemoresistance through genetic and/or epigenetic regulation of multiple signaling pathways. Some major genetic and epigenetic factors are illustrated in the figure (see text for detailed discussion).
\textbf{Abbreviations:} ALDH1, aldehyde dehydrogenase 1 family member A1; ATG7, autophagy associated gene; BRCA2, breast cancer susceptibility proteins 2; CTR1, copper transporter 1; ERCC1, excision repair cross-complementing rodent repair deficiency, complementation group 1; GSH, glutathione; GST, glutathione S-transferase; HR, homologous recombination; MMR, mismatch repair; MRP, multidrug-resistant-associated protein; NER, nucleotide excision repair; γ-GCS, \textgamma-glutamylcysteine synthetase.
\end{figure}
IncRNA and cisplatin resistance

As stated above, numerous studies over the years have demonstrated that lncRNAs play a significant role in chemoresistance. Aiming to understand the roles and mechanisms of lncRNAs in cisplatin resistance, we searched PubMed for all articles associated with “lncRNA and cisplatin resistance” and found that 22 lncRNAs have been reported to play an important role in cisplatin resistance through various mechanisms in multiple cancers (Table 1; Figure 2).

Influx/efflux of cisplatin

Previous studies have indicated that reduced drug uptake or increased drug efflux in cancer cells, which results in a reduced intracellular platinum accumulation, is an important biochemical and cytological mechanism of cisplatin resistance. ATP-binding cassette transporters, including P-glycoprotein and MRPs, can increase the drug efflux. Hang et al have reported that Notch 1 could promote cisplatin resistance in gastric cancer (GC) through upregulation of lncRNA AK022798 expression. When lncRNA AK022798 was knocked down, the expression of MRP1 and P-glycoprotein MDR1, two membrane drug efflux-porters, was significantly decreased, while cell apoptosis, caspase-3, and caspase-8 activities were significantly increased in SGC7901 and BGC823 cisplatin-resistant cancer cells. These results indicated that lncRNA AK022798 is a crucial mediator in Notch 1-induced cisplatin resistance in cancer cells. In GC tissues and cells, high expression of lncRNA PVT1 was significantly associated with the development of cisplatin resistance. PVT1 silencing could reverse the cisplatin resistance in cisplatin-resistant cell lines, while upregulation of PVT1 decreased the sensitivity of parental GC cells to cisplatin, which was mediated through upregulation of MDR1, MRP, mTOR, and HIF-1a expression. The lncRNA ANRIL has also been reported to be highly expressed in...
cisplatin-resistant and 5-fluorouracil-resistant GC tissues and cells. Further studies have revealed that ANRIL knockdown might inhibit cell proliferation and invasion, promote anticancer agent-induced apoptosis, and reverse drug resistance in cisplatin- and 5-fluorouracil-resistant GC cell lines by downregulating MDR-related gene expression, including MDR1 and MRPI. ANRIL, a copper influx transporter, plays a vital role in platinum drug uptake and the development of cisplatin resistance. The lncRNA ANRIL participates in the process of cisplatin resistance. The lncRNA ANRIL was associated with cisplatin resistance, and GSH depletion increased sensitivity to cisplatin. As such, overexpression of enzymes involved in GSH synthesis and metabolism participates in the process of cisplatin resistance. The lncRNA ANRIL was overexpressed in ovarian cancer tissues and correlated with cancer recurrence, whereas H19 knockdown in A2780-DR cells increased their sensitivity to cisplatin treatment with a lower GSH level. H19 contributed to cisplatin resistance by regulating NRF2 and its target proteins which are involved in the GSH metabolism pathway.

**Intracellular detoxification**

GSH is a kind of metallothionein, which shows a much higher affinity to cisplatin than DNA. Increased GSH synthesis was associated with cisplatin resistance, and GSH depletion increased sensitivity to cisplatin. As such, overexpression of enzymes involved in GSH synthesis and metabolism participates in the process of cisplatin resistance. The lncRNA H19 was overexpressed in ovarian cancer tissues and correlated with cancer recurrence, whereas H19 knockdown in A2780-DR cells increased their sensitivity to cisplatin treatment with a lower GSH level. H19 contributed to cisplatin resistance by regulating NRF2 and its target proteins including NQO1, GSR, G6PD, GCLC, GCLM, and GSTP1, which are involved in the GSH metabolism pathway.

### Table 1 Predictive lncRNAs involved in response to cisplatin

<table>
<thead>
<tr>
<th>lncRNAs</th>
<th>Role in response</th>
<th>Targets</th>
<th>Mechanisms</th>
<th>Cancers</th>
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<tr>
<td>AC023115.3</td>
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<td>HOTAIR</td>
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<td>By decreasing IκBα</td>
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<td>hnRNP-U/ADD45A</td>
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<td>R</td>
<td>mir-196a</td>
<td>Affecting transcription by activating CREB</td>
<td>Bladder cancer</td>
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<td>mir-17/ATG7</td>
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**Abbreviations:** ABCB1, ATP-binding cassette subfamily B member 1; ABCG2, ATP-binding cassette subfamily G member 2; ceRNA, competing endogenous RNA; CReB, cAMP response element-binding protein; CTR1, copper transporter 1; lncRNAs, long non-coding RNAs; LSCC, lung squamous cell carcinoma; MDR1, multidrug-resistant protein; MRPI, multidrug-resistant-associated protein 1; N/A, not available; NEAT1, nuclear-enriched abundant transcript 1; NSCLC, non-small-cell lung cancer; P-gp, P-glycoprotein; R, resistance; Ref, reference; S, sensitivity.
DNA repair and cell cycle

Nuclear factor-κB (NF-κB) signaling-mediated activation of DNA damage response plays a role in the development of cell resistance to cisplatin. The IncRNA HOTAIR overexpression induced cisplatin resistance in ovarian cancer cells and resulted in sustained activation of DNA damage response after cisplatin treatment through NF-κB activation due to Iκ-Bα (NF-κB inhibitor) downregulation. Collectively, these data suggest that HOTAIR contributes to chemoresistance through DNA damage-induced NF-κB signaling pathways. HOTAIR has also been reported to promote cisplatin resistance by regulating p21WAF1, a cyclin-dependent kinase inhibitor which inhibits cell proliferation by inducing G0/G1 arrest, in lung adenocarcinoma (LAD) cells.

In nasopharyngeal carcinoma (NPC) cells, knockdown of lncRNA ANRIL inhibited cell proliferation, while it induced cell apoptosis and potentiated cisplatin-induced DNA damage by regulating microRNA let-7a expression.

Apoptosis

As cisplatin-induced DNA damage causes cell apoptosis, inhibition of apoptosis may also be involved in the acquired cisplatin resistance. p53, a tumor suppressor gene, plays a critical role in the apoptosis pathway. Several studies have shown that lncRNAs were associated with the cisplatin chemoresistance by downregulating p53-induced cell apoptosis. The lncRNA p53-dependent apoptosis modulator (PDAM) silencing induced cisplatin resistance in glioma cells by harboring wild-type p53, while BCL2L1 knockdown in PDAM-suppressed cells abrogated the cisplatin-resistant phenotype. These data indicate that PDAM regulated cisplatin resistance by regulation of p53-dependent antia apoptotic genes (OTs). The long non-coding RNA regulator of reprogramming (lncRNA-ROR), which played a crucial role in cell proliferation, migration, and apoptosis of NPC, promoted cisplatin resistance in NPC by improving cell proliferation and reducing cell apoptosis mediated by p53 signaling pathways.

In A549 cisplatin-resistant cells, lncRNA MEG3 expression was significantly downregulated and overexpression of MEG3 restored cell sensitivity to cisplatin by suppressing cell proliferation and inducing apoptosis and cell cycle arrest. Further studies elucidated that MEG3-mediated chemosensitivity was associated with the WNT/β-catenin signaling pathway by regulation of p53, as well as with the mitochondrial apoptosis pathway.

In addition, Ma et al have revealed that downregulation of lncRNA TRPM2-AS inhibited cisplatin resistance, induced cell apoptosis, and altered cell cycle distribution in NSCLC through activating the p53-p66Shc pathway.

The Bcl-2 family is a key member in mitochondrial apoptosis pathway, which consists of the antia apoptotic family...
(such as BCL-2 and BCL-XL), the proapoptotic family (BAX and BAK), and the proapoptotic BH3-only protein family (such as BAD, BIK).\textsuperscript{57} The IncRNA H19 contributed to cisplatin resistance in LAD by promoting cell migration via vimentin and reducing apoptosis via FAS, BAK, and BAX. The clinical study has shown that in patients with LAD, a high tumor H19 expression was negatively correlated with cisplatin-based chemotherapy response and a significantly shorter median progression-free survival, which were consistent with the data in in vitro experiment.\textsuperscript{58} The IncRNA ENST00000457645 could remarkably reverse cisplatin resistance by promoting apoptosis of cisplatin-resistant CP70 cells, which was associated with altered levels of apoptosis proteins such as Bax and cleaved caspase-3.\textsuperscript{59}

The IncRNA PVT1 was upregulated in ovarian cancer tissues from cisplatin-resistant patients and in cisplatin-resistant cells. PVT1 overexpression promoted cisplatin resistance through regulating the expression of TGF-β1, p-Smad4, and caspase-3, molecules related to the apoptotic pathways.\textsuperscript{60} The upregulation of UCA1 IncRNA contributed to cisplatin resistance by promoting cancer cell proliferation while inhibiting apoptosis in bladder cancer and cervical cancer cells.\textsuperscript{61} In human bladder cancer cells, UCA1-mediated chemosensitivity was associated with the apoptosis pathway by upregulating miR-196a-5p targeting p27\textsuperscript{58}p1.\textsuperscript{61} In cervical cancer cells, UCA1 suppressed cell apoptosis by downregulating caspase-3 and upregulating CDK2, whereas cell proliferation was enhanced through inducing survivin and decreasing p21 expression.\textsuperscript{62} In ovarian cancer cells, curcumin-induced MEG3 IncRNA expression due to demethylation was directly associated with a decrease in miR-214 and extracellular vesicle-mediated transfer of miR-214, resulting in an elevation of cisplatin-induced cell apoptosis and cell sensitivity to cisplatin-based chemotherapy.\textsuperscript{63} The IncRNA SFTA1P increased cisplatin chemosensitivity by enhancing cisplatin-induced apoptosis by increasing the expression of hnrNP-U and GADD45A in lung squamous cell carcinoma.\textsuperscript{64}

It has also been reported that IncRNAs CUDR, HOTAIR, and HULC modulated cisplatin resistance through alteration of cell apoptosis, but their exact molecular mechanisms remain to be elucidated.\textsuperscript{65-67} Wang et al\textsuperscript{65} have reported that IncRNA CUDR (UCA1a) played a pivotal role in bladder cancer progression, and promoted cell proliferation, migration, and invasion in UM-UC-2 cells. In addition, CUDR overexpression might contribute to cisplatin resistance by antagonizing apoptosis.\textsuperscript{65} HOTAIR also promoted cisplatin resistance in ovarian carcinoma. The knockdown of HOTAIR suppressed cell proliferation and invasion, and notably increased chemosensitivity to cisplatin specifically by promoting cisplatin-induced apoptosis in SKOV-3 cisplatin-resistance cells.\textsuperscript{66} Patients with a high expression of HULC IncRNA in GC showed a significantly worse prognosis, and HULC knockdown enhanced the sensitivity of GC cells to cisplatin by enhancing cisplatin-induced apoptosis.\textsuperscript{67}

### Signaling pathways

Studies over the years have demonstrated that diverse signaling pathways are involved in the development of drug resistance.\textsuperscript{68} Analysis of mRNA, IncRNA, and miRNA expression profiles by microarray in cisplatin-resistant A549 cells and parental A549 cells revealed that 1,471 mRNAs, 1,380 IncRNAs, and 25 miRNAs were differentially expressed.\textsuperscript{69} Gene coexpression network analysis identified many genes including IncRNA AK126698 that potentially play a significant role in cisplatin resistance.\textsuperscript{69} Pathway analysis showed that the Wnt pathway was targeted by both miRNAs and IncRNAs including IncRNA AK126698. Moreover, in vitro cell culture experiments confirmed that AK126698 IncRNA induced cisplatin resistance in NSCLC through activating Wnt/β-catenin pathway.\textsuperscript{69} UCA1 IncRNA expression levels were significantly higher in T24-resistant cells and bladder cancer tissues from patients treated with cisplatin, and overexpression of UCA1 IncRNA promoted cisplatin resistance in bladder cancer cells through upregulating Wnt6 expression, which consequently activated Wnt signaling.\textsuperscript{70} The IncRNA HOTTIP could promote cell proliferation, cell cycle progression, and induce cell resistance to cisplatin by activating the Wnt/β-catenin pathway in osteosarcoma and ovarian cancer cells.\textsuperscript{71}

### Autophagy

Autophagy plays an important role in the maintenance of cell hemostasis, and LC3, Beclin-1, and Atg family members are important factors in autophagosome formation.\textsuperscript{72} Recently, several studies have reported that autophagy could act as a protective mechanism against cisplatin treatment in cancer cells.\textsuperscript{73} Like 3-MA, an autophagy inhibitor, IncRNA GAS5 was shown to inhibit autophagy and, therefore, enhance cell sensitivity to cisplatin in NSCLC cells.\textsuperscript{73} In human endometrial cancer cells, HOTAIR IncRNA contributed to cisplatin resistance by regulating autophagy mediated through the regulation of Beclin-1 expression.\textsuperscript{74} The IncRNA XIST was upregulated in NSCLC cells and promoted the progression of NSCLC through regulating autophagy. Knockdown of XIST enhanced the chemosensitivity to cisplatin in NSCLC.
cells, which was reversed by the administration of a miR-17 inhibitor and overexpression of ATG7, a key factor in autophagosome formation. These data suggest that lncRNA XIST enhanced the chemoresistance of NSCLC cells to cisplatin by regulating autophagy via the miR-17/ATG7 pathway. In human glioblastoma cells, the upregulation of lncRNA AC023115.3 promoted chemosensitivity to cisplatin by decreasing autophagy. Further mechanism experiments showed that AC02115.3 acted as a miR-26a sponge and increased its target gene GSK3β expression.

Cancer stem cells (CSCs)
CSCs are a small population of specialized cells that have the potential to self-renew and differentiate into other tumor cell subtypes and are involved in tumor initiation, progression, distant metastasis, and chemoresistance. Emerging evidence indicates that lncRNAs play an important role in the maintenance of CSCs, increasing tumor cells’ resistance to chemotherapy. HOTAIR lncRNA could promote tumorigenesis and tumor metastasis by affecting the stemness of CSCs. Moreover, Liu et al have found that HOTAIR contributed to cisplatin resistance by regulating the biology of tumor stem cells. HOTAIR was overexpressed in tumor tissues from NSCLC patients with drug resistance and in cisplatin-resistant A549 cells, and knockdown of HOTAIR expression increased the sensitivity of A549/cisplatin cells to cisplatin. Further mechanistic studies demonstrated that HOTAIR-induced cisplatin resistance might be associated with the promotion of tumor sphere cell growth through upregulating tumor stem cell-related Klf4 expression.

ceRNAs
In recent years, accumulating evidence indicates that lncRNAs, such as ceRNAs, could regulate target mRNA levels by combining competitively with common miRNAs, which is a potential mechanism in the regulation of cisplatin resistance. The lncRNA NEAT1-enhanced cisplatin sensitivity was mediated through upregulating EGCG-induced CTR1 expression due to its sponging action on mir-98-5p in lung cancer cells. The lncRNA LINC00161 promoted cisplatin-induced apoptosis and decreased cell resistance to cisplatin. Further studies revealed that the effect of LINC00161 was achieved through upregulation of IFIT2 protein expression mediated via competitively sponging miR-645 action on IFIT2 mRNA. Moreover, other lncRNAs such as CASC, GAS5, and MEG3 have also been reported to function as ceRNAs of miR-21 and miR-21-5p and upregulate PTEN and SOX7 expression, respectively, in NSCLC and cervical cancer cells, resulting in an alteration of cell sensitivity to cisplatin. In glioma cell, lncRNA AC023115.3 acted as a ceRNA for miR-26a and attenuated the inhibitory effect of miR-26a on GSK3β, which impaired cisplatin resistance.

Conclusion
Cisplatin resistance, either intrinsic or acquired, is a significant burden for successful cancer treatment. Here, we have discussed the roles of lncRNAs in cisplatin chemoresistance (Table 1) through mechanisms such as alterations in cellular uptake or efflux of the drug, intracellular detoxification, cell apoptosis, autophagy, DNA repair, CSC, and ceRNA action (Figure 2). Although the study of lncRNAs on chemoresistance is still in its infancy, growing evidence suggests that lncRNAs may serve as biomarkers for cancer diagnosis and prognosis and molecular targets for cancer therapy, including chemoresistance. BC-819 (H19-DTA) is a DNA vector that carries the gene for diphtheria toxin-A under the control of the H19 promoter sequence, which therefore has the potential to treat various malignancies that overexpress H19 lncRNA. Current clinical trials indicate that BC-819 given locally in combination with systemic chemotherapy may provide an additional therapeutic benefit for the treatment of pancreatic, bladder, ovarian, or peritoneal cancer.

Of course, considerable work needs to be done for the lncRNA-based cancer therapy to be applied in clinical practice. First, chemoresistance is a complicated biologic process in which the roles and mechanisms of lncRNAs are still poorly understood. The majority of studies are in in vitro systems. Second, informative functional studies rely on animal experiments. However, establishing lncRNA function model in mice is difficult. Third, the sequence conservation of lncRNAs is much poorer than that of protein-coding genes. Thus, the lncRNAs which have been successfully verified in animal models may be not able to translate into clinical practice. Fourth, as a therapeutic strategy, the technology for either elimination or overexpression of a specific lncRNA at specific target cells in vivo is still in development. Finally, it is currently unclear whether interference of an endogenous lncRNA expression in the body will generate deleterious biologic consequence. Nevertheless, studies over the last decades have provided sufficient data to warrant further investigation of lncRNAs on tumorigenesis, tumor progression, and tumor chemoresistance.

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Disclosure

The authors report no conflicts of interest in this work.

References


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