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The Role of LINC02381 in Modulating Cisplatin Resistance in Ovarian Cancer: A Bioinformatics Approach

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ABSTRACT

Cisplatin resistance presents a significant challenge in cancer therapy, emphasizing the necessity for identifying new regulatory elements that influence drug response. Recent research has revealed the importance of long noncoding RNAs (lncRNAs) in chemotherapy resistance, with *LINC02381* identified as a potential regulatory factor.

Through an in-depth bioinformatics analysis, we investigated the impact of *LINC02381* on cisplatin resistance in ovarian cancer across various datasets. By conducting differential expression analysis, survival analysis, gene set enrichment analysis (GSEA), and constructing protein-protein interaction (PPI) networks, we identified key pathways associated with *LINC02381* expression.

The results indicated that the altered expression of LINC02381 in patients treated with cisplatin was associated with reduced survival. Functional studies and correlation analyses further demonstrated that this LncRNA influences critical pathways and genes related to apoptosis, efflux, DNA repair, and EMT. Lastly, through an examination of its interactions with microRNA and protein networks, we identified *LINC02381* as a ceRNA implicated in cisplatin resistance.

Our findings suggest that *LINC02381* may influence cisplatin sensitivity in ovarian cancer and establish a basis for further experimental validation, including molecular assays or in vivo analyses, and suggest the potential therapeutic targeting of *LINC02381* to combat chemoresistance.

Keywords: Bioinformatics analysis; Chemoresistance; Cisplatin; *LINC02381*; Ovarian cancer

INTRODUCTION

Cancer is a condition marked by the unregulated proliferation of a cluster of cells that encroaches upon adjacent tissues and may occasionally disseminate to other regions of the body through the bloodstream or lymphatic system.[1] Cancer represents one of the most significant health challenges on a global scale. In 2021, approximately 15% of all deaths were attributed to cancer, positioning it as one of the leading causes of death worldwide.[2] Many cancers initially exhibit a favorable response to chemotherapy, effectively inhibiting tumor growth. However, after approximately

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6 months of treatment, patients frequently develop resistance to the medication, which typically shortens their survival to less than five years.[3] Cisplatin is one of the most prominent first-generation chemotherapy agents utilized against various cancer types. Despite its efficacy in treatment, the emergence of acquired resistance to cisplatin significantly reduces survival rates among patients with numerous cancer forms, such as ovarian cancer.[4] Thus, the identification of new biomarkers is essential for overcoming drug resistance to this vital chemotherapy drug. Recent research underscores the regulatory functions of long noncoding RNAs (lncRNAs) in a variety of genes and signaling pathways associated with drug resistance. Increasing evidence suggests that lncRNAs contribute to chemotherapy resistance by modulating gene expression, remodeling chromatin, and affecting various signaling pathways.[5] Therefore, investigating the interactions between noncoding RNAs and coding RNAs may reveal the molecular mechanisms that drive drug resistance in cancers. *LINC02381* is a noncoding RNA involved in several oncogenic processes,[6–9] yet its specific role in mediating cisplatin resistance is not well understood. This study aims to elucidate the function of *LINC02381* in regulating sensitivity to cisplatin using a bioinformatics-based approach.

MATERIALS AND METHODS

Data Collection

Gene expression profiles and clinical data were obtained from The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO) databases. Cisplatin response information was extracted from patient cohorts. To improve transparency in our data selection methodology, we have outlined comprehensive criteria for selecting publicly accessible RNA-seq, DNA-seq, and ChIP-seq datasets utilized in this research. Our focus was on datasets that represent both cisplatin-resistant and cisplatin-sensitive ovarian cancer cell lines, specifically emphasizing quality metrics such as read depth, alignment efficiency, and reproducibility among biological replicates. These criteria were essential for guaranteeing that our bioinformatics analyses were both dependable and relevant to the aims of our study.

Differential Expression Analysis

RNA sequencing data from cisplatin-sensitive and resistant tumor samples were analyzed using DESeq2 to identify differentially expressed genes (DEGs) associated with *LINC02381*.

Survival Analysis

Kaplan-Meier survival analysis was performed using the R package survival to assess the prognostic significance of *LINC02381* in cisplatin-treated ovarian cancer patients. Statistical significance was determined using the log-rank test.

Functional Enrichment Analysis

To identify pathways associated with *LINC02381*, gene set enrichment analysis (GSEA) was conducted on samples with high and low expression of *LINC02381*, utilizing Hallmark and KEGG gene sets. Gene ontology (GO) was performed to identify the biological processes, cellular components, and molecular functions enriched in *LINC02381*-associated genes.

Protein-Protein Interaction (PPI) Network

A protein-protein interaction (PPI) network of *LINC02381*-associated genes was constructed using the STRING database and visualized using Cytoscape to identify key molecular interactions.

Correlation Analysis

Pearson correlation coefficient was used to assess the relationship between *LINC02381* and genes involved in apoptosis, Wnt signaling pathway, drug efflux, and EMT pathways. The statistical significance of each correlation was determined using a 2-tailed *t* test, and *p* values were adjusted for multiple testing using the Benjamini-Hochberg method to control the false discovery rate. Only correlations with an adjusted *p* value<0.05 were considered statistically significant. These analyses were performed to identify potential functional links between *LINC02381* and these critical cellular processes.

MicroRNA Regulatory Network Analysis

microRNA (miR)-mRNA binding relationships were predicted using miRMap, miRanda, TargetScan, and miTarBase. The overlapping targets from at least two algorithms were considered for further analysis to minimize false positives. These interactions were then filtered based on various criteria, including binding energy, sequence complementarity, and evolutionary conservation.

Mutation and Copy Number Variation Analysis

Mutational landscape and copy number variation (CNV) data were extracted from TCGA to investigate genetic alterations associated with *LINC02381* expression. Furthermore, copy number alterations (CNAs), including amplifications and deletions, encompassing *LINC02381* were examined for correlations with *LINC02381* expression levels. The impact of specific mutations and CNAs on *LINC02381* expression was assessed using statistical methods, such as correlation analyses and differential expression analyses, to identify significant associations. These analyses aimed to uncover potential genetic drivers of *LINC02381* dysregulation in cancer.

Drug Sensitivity Analysis

The correlation between *LINC02381* expression and drug response was analyzed using pharmacogenomics datasets such as the Genomics of Drug Sensitivity in Cancer (GDSC) database. Statistical methods, including t-tests and ANOVA, were employed to determine if significant differences in drug response existed between the high and low *LINC02381* expression groups.

RESULTS

LINC02381 Overexpression Carries Prognostic Significance in Ovarian Cancer

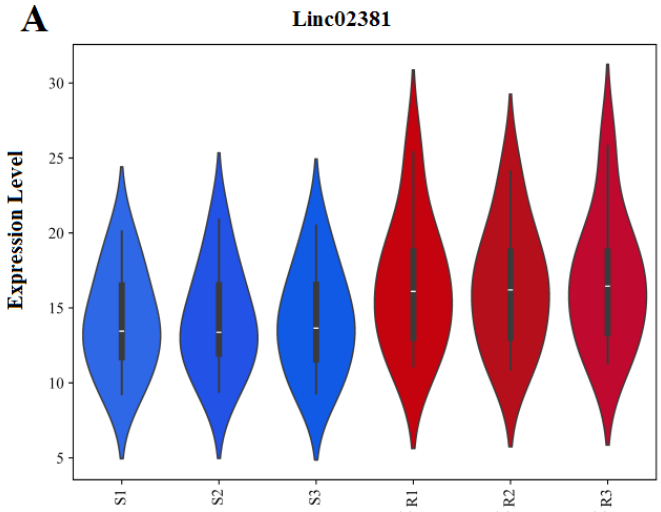
LINC02381 was significantly upregulated in cisplatin-resistant samples compared to sensitive ones (p<0.01) (Figure 1A). Gene expression profiling revealed co-expression with pivotal oncogenes, such as *TP53, ABCB1, CTNNB1,* and *BCL2* are associated with cisplatin resistance. Elevated *LINC02381* expression correlated with poorer overall survival in ovarian cancer patients treated with cisplatin (p=0.025) (Figure 1B). Stratified analysis across ovarian cancer confirmed its extensive impact on prognosis.

Functional Enrichment Analysis Links LINC02381 to Chemoresistance-Related Pathways

GSEA revealed enrichment of DNA repair, epithelial-mesenchymal transition (EMT), Wnt signaling pathway, and drug metabolism pathways in *LINC02381*-high samples. Pathways related to cell cycle progression and autophagy were also significantly upregulated (Figure 2A). Furthermore, functional enrichment analysis demonstrated that *LINC02381* influences transcriptional regulation, chromatin remodeling, and oxidative stress responses, which are critical in drug resistance adaptation (Figure 2B).

Protein-protein Interaction and MicroRNA Regulatory Network Analysis and Module Detection

Key interacting proteins included B-cell lymphoma 2 (BCL2), BCL2-associated X (BAX), catenin beta 1 (CTNNB1), and ATP-binding cassette (ABC) transporters, indicating a potential role of *LINC02381* in modulating apoptosis, Wnt signaling, and drug efflux. Network topology analysis identified hub genes central to chemoresistance mechanisms (Figure 3A). Predicted miR interactions with selected genes suggest *LINC02381* may act as a competitive endogenous RNA (ceRNA) by sponging *miR-150*, *miR-28*, and *has-let7b*, key regulators of cisplatin resistance (Figure 3B).



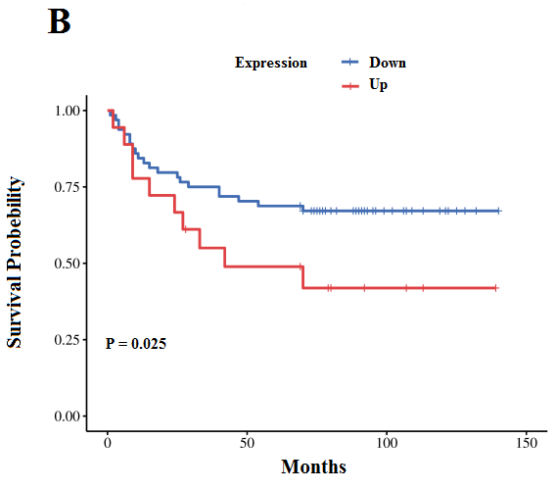


Figure 1. A. Long intergenic non-protein coding RNA 2381 (*LINC02381*) differential expression in cisplatin-sensitive (blue) and cisplatin-resistant (red) samples. *LINC02381* expression is elevated in resistant samples compared to sensitive ones. B. The survival rate of ovarian cancer patients changes with *LINC02381* expression. *LINC02381* overexpression leads to a reduced overall survival rate in ovarian cancer patients.

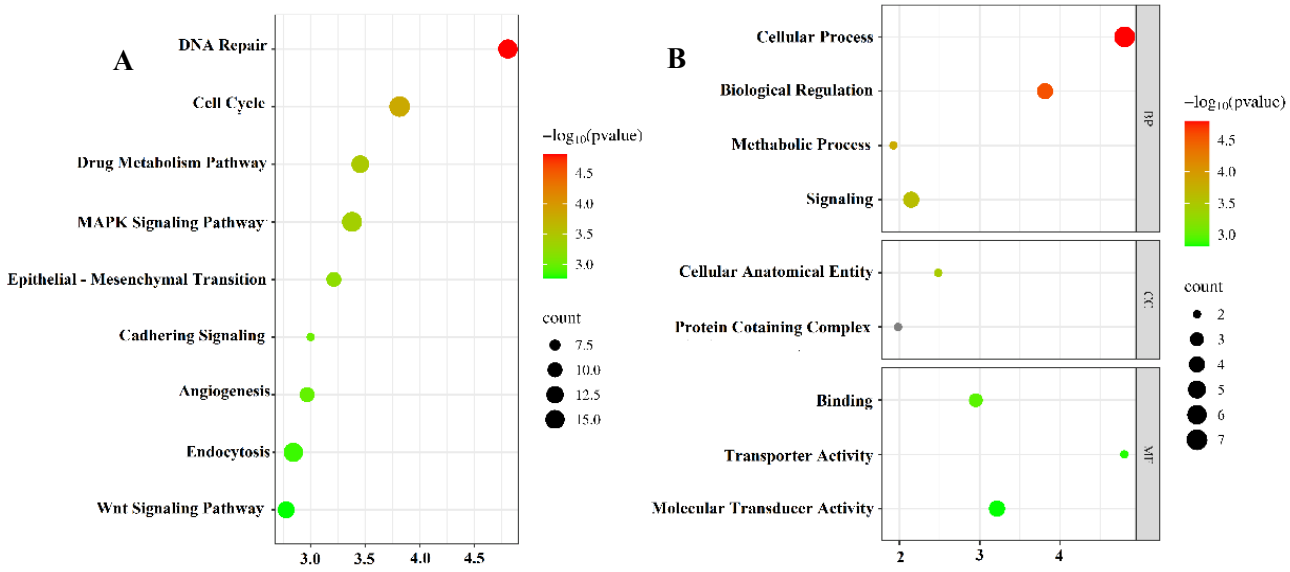


Figure 2. A. Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis of differentially expressed genes between cisplatin-resistant and sensitive samples. B. Gene ontology (GO) enrichment analysis of differentially expressed genes between cisplatin-resistant and sensitive samples.

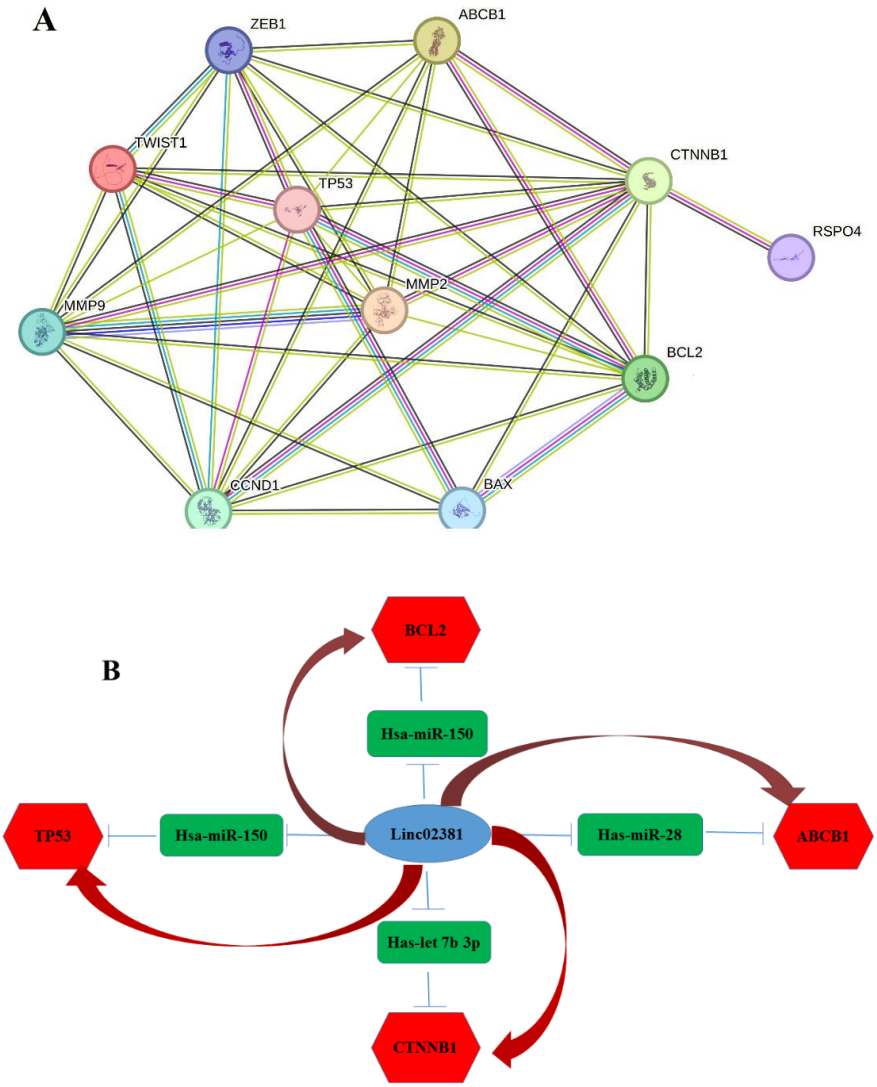


Figure 3. A. Protein-protein interaction network among the primary differentially expressed genes associated with cisplatin resistance. B. Proposed ceRNA networks comprising *LINC02381*, suggested microRNAs, and genes.*ABCB1*: ATP binding cassette subfamily B member 1; APC: APC regulator of WNT signaling pathway; *BAX*: *BCL2* associated X, apoptosis regulator; *BCL2*: B-cell lymphoma 2; *CCND1*: cyclin D1; ceRNA: competing endogenous RNA; *CTNNB1*: catenin beta 1; LINC02381: long intergenic non-protein coding RNA 2381; *MMP2*: matrix metallopeptidase 2; *MMP9*: matrix metallopeptidase 9; PPI: protein-protein interaction; *SNAI1*: snail family transcriptional repressor 1; *TP53*: tumor protein p53; *TWIST1*: twist family bHLH transcription factor 1; *ZEB1*: zinc finger E-box binding homeobox 1.

LINC02381 Correlates with the Main Genes Involved in Chemoresistance

Pearson correlation coefficient analysis indicated that *LINC02381* expression is significantly positively correlated with *CTNNB1* (r=0.063) (Figure 4A), tumor protein p53 (*TP53*) (r=0.052) (Figure 4B), *BCL2* (r=0.063) (Figure 4C), and *ABCB1* (r=0.06) (Figure 4D), highlighting its potential involvement in drug resistance mechanisms.

Mutation and Copy Number Variation Analysis

Somatic mutation analysis revealed significant alterations in genes co-expressed with *LINC02381*, particularly in apoptosis, DNA repair pathways, Wnt signaling, and efflux pumps. Copy number variation analysis indicated potential gene amplification in resistant samples (Figure 5).

Drug Sensitivity Analysis Indicated a Correlation between LINC02381 and the Toxic Effects of Cisplatin

An examination of pharmacogenomics data from http://www.jianglab.cn/ncRNADrug demonstrated that elevated *LINC02381* expression was associated with decreased sensitivity to cisplatin and other platinum-based drugs (Figure 6).

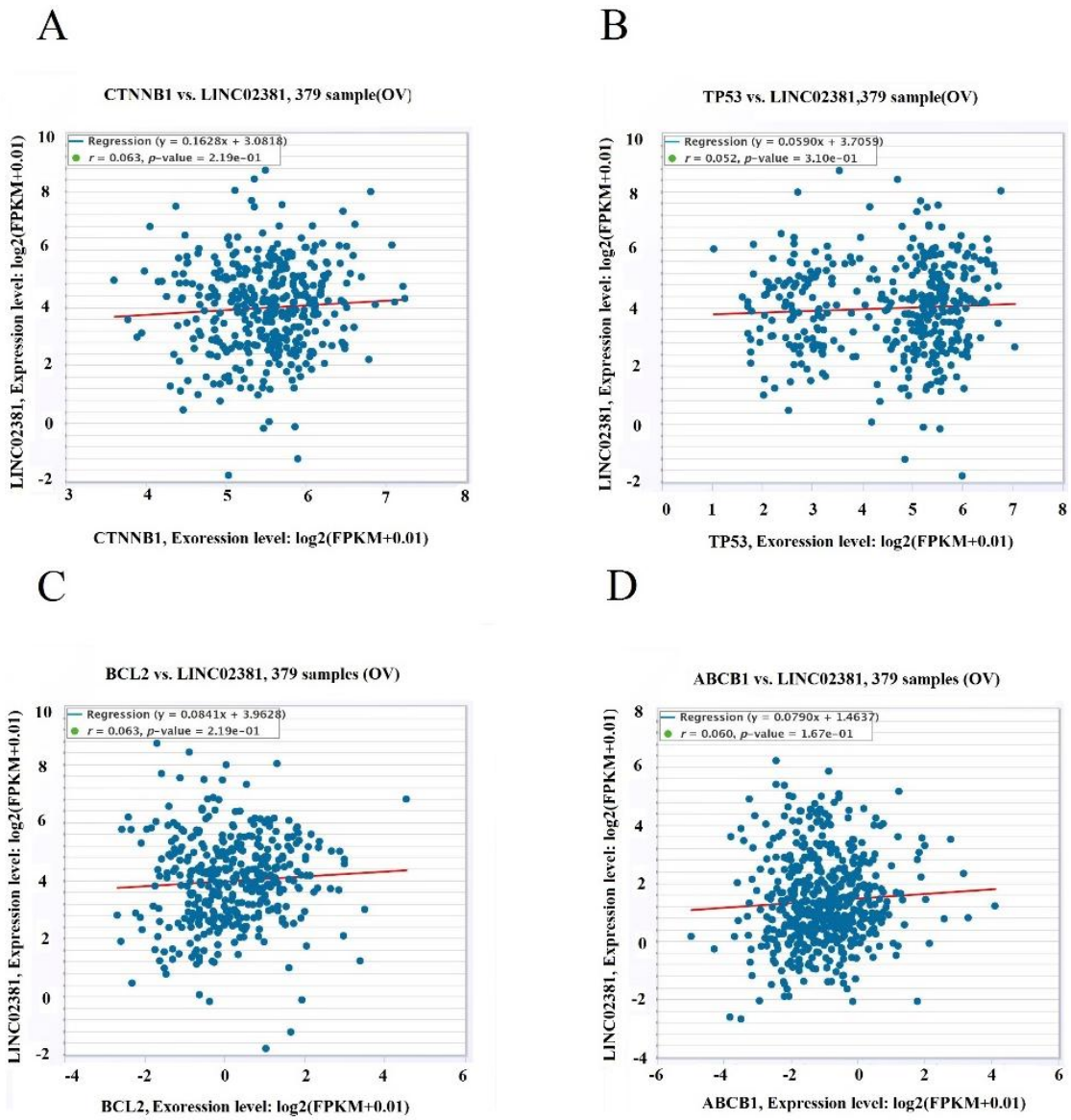


Figure 4. Pearson correlation analysis between *LINC02381* and *CTNNB1* (A), *TP53* (B), *BCL2* (C), and *ABCB1* (D). All of these oncogenes have a positive correlation with *LINC02381* expression. *ABCB1*: ATP-binding cassette subfamily B member 1; *BCL2*: B-cell lymphoma 2; *CTNNB1*: catenin beta 1; *LINC02381*: long intergenic non-protein coding RNA 2381; OV: ovarian cancer; TCGA: The Cancer Genome Atlas; *TP53*: tumor protein p53.

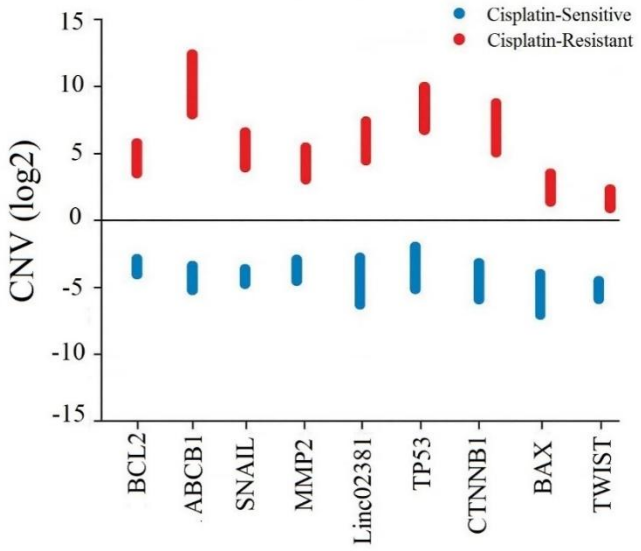


Figure 5. Analysis of the relationship between copy number variation (CNV) and differential gene expression. *ABCB1*: ATP binding cassette subfamily B member 1; *BAX*: *BCL2* associated X, apoptosis regulator; *BCL2*: B-cell lymphoma 2; *CTNNB1*: catenin beta 1; *LINC02381*: long intergenic non-protein coding RNA 2381; *MMP2*: matrix metallopeptidase 2; *SNAI1*: snail family transcriptional repressor 1; *TP53*: tumor protein p53; *TWIST1*: twist family bHLH transcription factor 1.

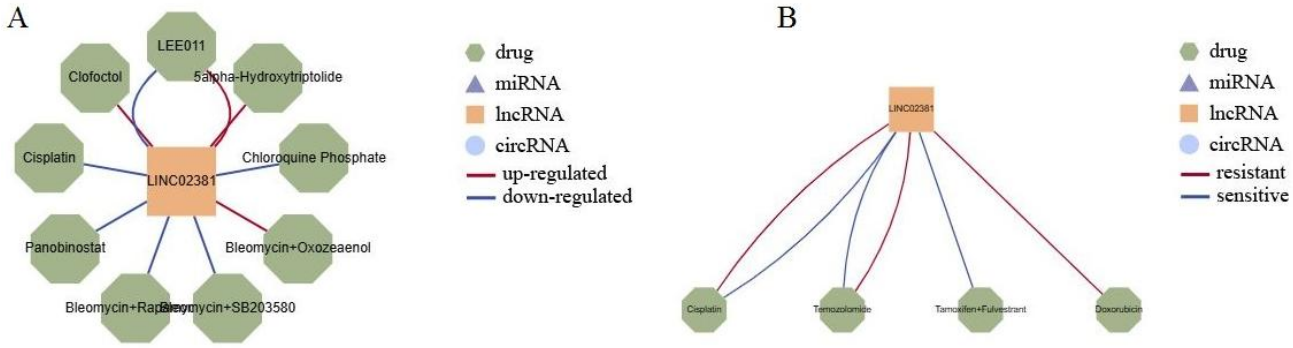


Figure 6. *LINC02381* interacts with cisplatin and other drugs. Its interaction is 2-way with cisplatin and Temozolomide. circRNA: circular RNA; LINC02381: long intergenic non-protein coding RNA 2381; lncRNA: long noncoding RNA; miRNA: microRNA. (http://www.jianglab.cn/ncRNADrug)

DISCUSSION

The identification and subsequent application of newly discovered long non-coding RNAs (lncRNAs), along with a deeper understanding of their various regulatory mechanisms, can significantly advance our ability to predict and potentially mitigate Cisplatin resistance in cancer patients. This development may pave the way for innovative options in adjuvant therapy, enhancing treatment regimens and improving patient outcomes. One particular lncRNA, known as LINC02381, has been identified as an oncogene in multiple forms of cancer. While it is established that LINC02381 functions as a competing endogenous RNA, the extent of its influence on the mechanisms behind Cisplatin resistance remains ambiguous and not fully understood.

Our research offers new perspectives on the function of *LINC02381* in influencing cisplatin resistance. The increased expression of *LINC02381* in resistant tumors, along with its association with unfavorable survival outcomes, highlights its potential as a prognostic

biomarker. The activation of DNA repair and epithelial-mesenchymal transition (EMT) pathways points to a possible mechanism by which *LINC02381* contributes to chemoresistance. These findings suggest a multifaceted role for *LINC02381* in promoting cancer cell survival and adaptation under therapeutic pressure. The activation of DNA repair mechanisms could enable cells to overcome drug-induced DNA damage, while EMT may facilitate metastasis and drug resistance acquisition. The upregulation of drug metabolism pathways might enhance the detoxification and elimination of chemotherapeutic agents, further contributing to resistance. The concurrent stimulation of cell cycle progression and autophagy, seemingly paradoxical, might reflect a complex interplay where autophagy supports cell survival by removing damaged organelles and proteins, allowing for continued proliferation even under stress. The influence of *LINC02381* on transcriptional Regulation and chromatin remodeling may highlight its potential to globally reprogram cellular processes, while its influence on oxidative stress responses indicates a role in alleviating the harmful effects of reactive oxygen species frequently produced during drug treatment. Moreover, its interactions with *CTNNB1*, *TP53*, *BCL2*, and *ABC* transporters can underscore its significance in drug response. However, the weak correlation coefficients suggest that the association, while statistically significant, may not be strong enough to individually drive significant changes in the expression of these genes. These findings suggest that *LINC02381* might exert its influence on drug resistance through a more complex mechanism, possibly by interacting with multiple pathways or acting as a modulator of other regulatory factors.

The regulatory network of miRs further bolsters the theory that *LINC02381* acts as a competing endogenous RNA (ceRNA), affecting critical miRs related to resistance. This ceRNA activity likely fine-tunes the expression of target genes involved in the Wnt signaling pathway, DNA repair, apoptosis, and efflux pumps, ultimately influencing the sensitivity or resistance of cells to various therapeutic agents. Dysregulation of *LINC02381*, therefore, could potentially shift the balance, favoring prosurvival pathways and contributing to the development of drug resistance in various cancers such as ovarian cancer. Exploration of *LINC02381*'s interaction is crucial to fully elucidate its mechanism of action. Identifying its binding partners, both RNA and protein, will provide a more comprehensive understanding of its influence on cellular processes relevant to cisplatin resistance. Specifically, investigating its impact on DNA repair mechanisms, apoptosis signaling, and drug transporter expression is warranted. Subsequent in vitro and in vivo experiments are needed to validate these bioinformatics-derived hypotheses, assessing the effects of *LINC02381* knockdown or overexpression on cisplatin sensitivity in cancer cell lines and animal models. Ultimately, this research could pave the way for novel therapeutic strategies targeting *LINC02381* to enhance the efficacy of cisplatin-based chemotherapy and improve patient outcomes.

This study identifies *LINC02381* as a potential regulator of cisplatin resistance through bioinformatics analysis. Its association with key oncogenic pathways and drug resistance mechanisms, along with its role in ceRNA networks, underscores its potential as a therapeutic target for overcoming chemoresistance. Dysregulation of *LINC02381* expression could disrupt the balance of ceRNA networks, leading to alterations in the expression of downstream target genes involved in cisplatin resistance. Future experimental validation is necessary to confirm its role in cancer treatment. Furthermore, investigating *LINC02381*'s interactions with other molecules and its impact on cellular processes may offer valuable insights into its function. Elucidating the specific mechanisms by which *LINC02381* influences these pathways could provide a more comprehensive understanding of its role in cancer chemoresistance. Further research should focus on exploring the therapeutic potential of targeting *LINC02381* to enhance the efficacy of cisplatin-based chemotherapy regimens and improve patient outcomes.

STATEMENT OF ETHICS

Not applicable.

FUNDING

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

Not applicable.

DATA AVAILABILITY

All data supporting the findings are available in the Supplementary Materials.

AI ASSISTANCE DISCLOSURE

Not applicable.

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