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KIAA0101 promotes cisplatin resistance through regulating cell apoptosis in lung cancer cells

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ABSTRACT

Lung cancer is one of the most server mortality in the world and remains a huge threat to human health. Recently, cisplatin-based chemotherapy represented a common therapeutic strategy, however, cisplatin resistance greatly limits the therapy efficacy. We investigated whether KIAA0101 plays a role in cisplatin resistance of lung cancer cells and its mechanisms of action. The expression of KIAA0101 was evaluated based on comprehensive bioinformatic analysis. KIAA0101 knockdown and overexpression A549 cells were constructed to investigate its effects on cell proliferation and apoptosis induced by cisplatin treatment. Western blot analysis was performed to measure the levels of p53-related apoptosis proteins. We found that KIAA0101 was greatly increased in lung cancer tissues and cells. Knockdown of KIAA0101 suppressed cell proliferation and increased cisplatin-induced apoptosis. Knockdown of KIAA0101 also augmented the cisplatin-induced cell apoptosis signaling pathway. Then p53 was found to account for the role of KIAA0101 in cisplatin resistance. In conclusion, our findings provide a novel factor of KIAA0101 in lung cancer resistance, which suggests as a novel target for lung cancer therapy.

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Introduction

As one of the leading causes of mortality across the world, lung cancer is an important threat to patient survival and affected life quality (1, 2), with an estimated 2 million new cases and 1.76 million death cases annually (3). Lung cancer is commonly divided into non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC) based on its clinical features and pathological classification, and most of the lung cancer cases are NSCLC (4). Currently, surgery, chemotherapy, radiotherapy, target therapy and immunotherapy represent the main treatment strategy for lung cancer treatment (5-9). Among all of these strategies, cisplatin-based chemotherapy is the best choice for a large percentage of patients (10, 11). However, acquired drug resistance limits the overall therapeutic efficacy and is closely related the treatment failure. It is required to develop novel targets for overcoming cisplatin resistance.

Apoptosis plays a crucial role in maintaining physiological homeostasis in cellular responses to potentially harmful or abnormal stimuli (12). When the apoptosis machinism fails, the abnormal cells can survive and lead to unopposed tissue growth, just linke cancer (13). Therefore, it is conceivable that cancer may be caused or enhanced in part by factors that inhibit cell death.

KIAA0101 is a proliferation cell nuclear antigen-associated factor and was found to be upregulated in many types of cancers as an oncogenic function, such as in hepatocellular carcinoma, pancreatic cancer, and esophageal cancer (14-16). Especially in lung cancer, KIAA0101 was found to be significantly upregulated which predicts poor outcomes for primary lung cancer patients (17). KIAA0101 was also found to interact with UbcH10 to regulate cell proliferation through disrupting the spindle assembly (18). KIAA0102 was also found to be related to cancer metastasis in NSCLC (19, 20). Notably, it has been reported that KIAA0101 can inhibit cisplatin-induced apoptosis in ovarian cancer cells, resulting in cisplatin resistance (21). However, the relationship of KIAA0101 in cisplatin resistance of lung cancer has not been reported.

In our present study, we first investigated whether KIAA0101 plays a role in cisplatin resistance of lung cancer cells. our findings revealed that KIAA0101 was significantly related to cancer proliferation and survival of lung cancer patients. Knockdown of KIAA0101 significantly augmented cisplatin-induced cell death, and reduced cell survival through facilitated cell apoptosis pathway. Our findings provided novel data supporting that KIAA0101 could be regarded as a novel target for conquering the cisplatin resistance of lung cancer.

Materials and Methods

Bioinformatic analysis

An online bioinformatic tool Gepia (http://gepia.cancer-pku.cn/) was used to analyze the overall expression of KIAA0101 in lung cancer tissues and normal tissues. The overall survival, as well as progression-free survival

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in KIAA0101 high and low patients, were analyzed with Gepia software by using a cutoff at medium parameters.

Cells and treatments

Human lung cancer cell lines A549, H1299, H358 and H460 cells, and Human bronchial epithelial cell line BEAS-2B were purchased from ATCC (Manassas, VA, USA). Cells were maintained in RMPI-1640 medium supplemented with 10% fetal bovine serum with antibiotics in a humidified incubator at 37 centigrade. Cells were plated into 25 cm^2 flask (Corning, USA) or 60mm dishes for expansion and passaged every 2-3 days. Cells were maintained in a healthy condition and used for further experiments.

Plasmids and transfection

For KIAA0101 knockdown, we designed a set of siRNAs and inserted them into a pLKO.1-puro-U6-shRNA plasmid, respectively. Then each knockdown plasmid was transfected into A549 cells with a Lipofectamine™ 3000 reagent (Invitrogen, USA) according to the manufacturer's instructions. At 48h after transfection, cells were selected with puromycin (Sigma, USA) at the concentration of 800 ug/mL for 7 days. The selected cells were confirmed for the knockdown efficacy and used for the next experiments. In the same way, the full sequence of KIAA0101 was cloned into pcDNA6 plasmid and transfected into A549 cells, which was also used for the next experiments.

Cell apoptosis assay

For cell apoptosis experiments, a commercial Annexin V and PI double staining kit (Beyotime, Haimen, China) were used for detecting apoptotic cells after different treatments. Briefly, at 24h after cells were exposed to cisplatin (Sigma, PHR1624) treatments (22), cells were collected and stained with Annexin V-FITC staining solution for 20 min in the dark. After that, cells were stained with PI and subjected to flow cytometry analysis (BD, USA).

Quantitative real-time PCR

Cells were harvested and total RNA was extracted using TRIzol reagent and quantified using a nanodrop2000 spectrophotometer (Thermo Fisher Scientific, USA). For RNA reverse transcription, cDNA was synthesized using the PrimeScript™ RT Master Mix (Perfect Real Time) Synthesis Kit (Takara, RR036A). For qRT-PCR analysis, CFX Connect quantitative PCR instrument (BIO-RAD, USA) was used for detection, KIAA0101 primer: forward primer: 5 '-CTCTGCCACTAATTCGACATCA-3', reverse primer: 5 '- TTCAGAATCTTTAGGGGACAAC - 3'; p53 primer: forward primer: 5 '-CGTGTCGGAGGAGGATAG-3', reverse primer: 5 '-AGCTGCTCTGGTTCTTGGAC-3'; GAPDH primer: forward primer: 5'-TGACTTCAACAGCGACACCCA-3', reverse primer: 5 '-CACCCTGTTGCTGTAGCCAAA-3'. Amplification conditions: predenaturation, 95°C for 30 seconds; PCR reaction: 95°C for 5 seconds; 60 °C for 30 seconds; 40 cycles. Bar graphs are the mean±SD of three separate experiments.

Western blotting assay

At different times after cisplatin treatment, cells were scratched and protein was extracted with a RIPA extraction buffer (Antoper Biotech. Co, Shanghai, China). Then the proteins were centrifuged at the speed of 14000g at 4 °C. After then proteins were subjected to SDS-PAGE and transferred to an Immobilon® - NC membrane (Millipore, Germany). Cell the protein was blocked in milk and incubated with primary antibodies including, Bcl-2 (CST, 1:2000), Bax (CST, 1:1000), cleaved-caspase 3 (CST, 1:1000), p53 (CST, 1:1000), Phospho-p53 (Ser20) Antibody (CST, 1:1000), p21(CST, 1:2000) and GAPDH (CST, 1:5000). After incubation, proteins were incubated with secondary HRP conjucted antibody and exposure in a Syngene capture machine (Syngene, USA).

CCK-8 assay

To detect the cell proliferation in and absent of cisplatin, cell proliferation was analyzed by using a CCK-8 kit according to the manufacturer's instructions (Antoper BioTech Co, Shanghai, China). Briefly, cells were seeded at the concentration of 5000 cells per well in the 96-well plates. At 24, 48 and 72h after cell plating, cells were stained with CCK-8 solution, and analyzed with a plate reader (BioTech, USA) at the absorbance of OD_{570}.

Statistical analysis

All the data were expressed as mean ± SD. Comparisons between two groups were performed by student *t*-tests. P-values less than 0.05 were considered significant. Analysis was performed by using GraphPad Prism 8.0 software. All the experiments were repeated for three independent times.

Results

Upregulation of KIAA0101 was closely correlated to the overall survival of patients

To study the correlation of KIAA0101 to the overall survival of lung cancer patients, we performed an informatic analysis in TCGA data from Gepia software. KIAA0101 was found significantly upregulated in tumor tissues than that in the adjacent normal tissues (Fig. 1A). Then survival analysis revealed that the expression of KIAA0101 was negatively correlated with overall survival as well as progression-free survival (Fig. 1B, C). After the information analysis, we checked the expression level of KIAA0101 in different lung cancer cell lines including A549, H1299, H358 and H460 cells compared with the normal lung cells of BEAS-2B. KIAA0101 was also upregulated in lung cancer cells (Fig. 1D).

Knockdown of KIAA0101 increased cellular sensitivity of lung cancer to cisplatin

To investigate the effects of KIAA0101 on cell proliferation and cisplatin sensitivity, KIAA0101 knockdown (Fig. 2A, B) and overexpression (Fig. 2C, D) A549 cells were constructed. Through CCK-8 assay at different times after cell plating, we found that KIAA0101 knockdown significantly inhibited cell proliferation of lung cancer cells compared with the NC group (Fig. 2E). While the KIAA0101 overexpression significantly increased cell proliferation compared with the vector group (Fig. 2F). To determine the influence of KIAA0101 on cisplatin sensitivity, survival assay with a survival curve was performed. Our results showed that KIAA0101 significantly suppressed the survival fraction of lung cancer cells when treated with cisplatin (Fig. 2G). On the other hand, KIAA0101 overexpression significantly enhanced cellular

resistance to cisplatin treatment (Fig. 2H).

KIAA0101 inhibited cell apoptosis induced by cisplatin treatment

After knowing the survival fraction changes from KIAA0101 treatment, we measured cell apoptosis with a flow cytometry method. Our results showed that KIAA0101 knockdown significantly facilitated cisplatin-induced cell apoptosis (Fig. 3A, B). KIAA0101 knockdown also reduced the overall survived cells (Double negative). In contrast, in KIAA0101 overexpression cells, cisplatin-induced cell apoptosis was significantly repressed (Fig. 3C, D), which suggests that KIAA overexpression might enhance survival fraction under cisplatin through regulating cell apoptosis.

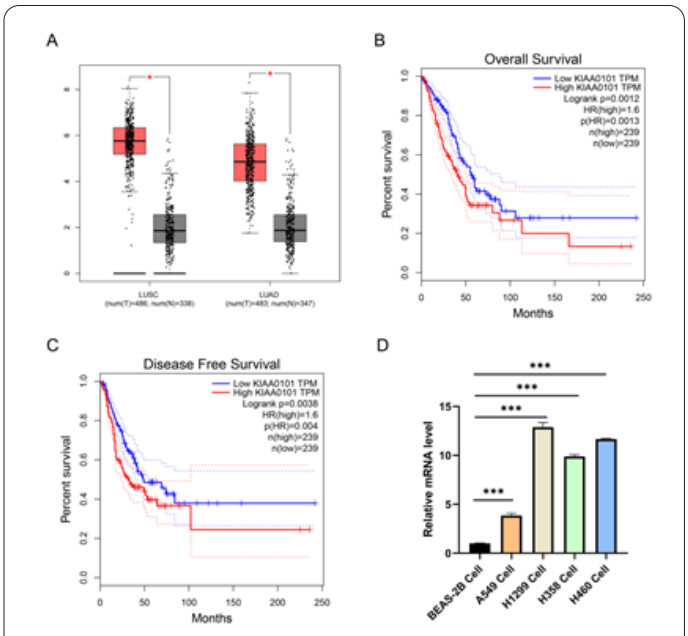

Figure 1. KIAA0101 expression is increased in TCGA LUSC and LUAD samples and has diagnostic value. (A) The expression of the prognosis of TCGA LUSC patients using the overall survival as well as progression-free KIAA0101 in 486 LUSC and 338 non-cancerous lung tissues. (B, C) Assessing survival. (D) The expression of the prognosis of lung cancer cell lines and the normal lung cells.

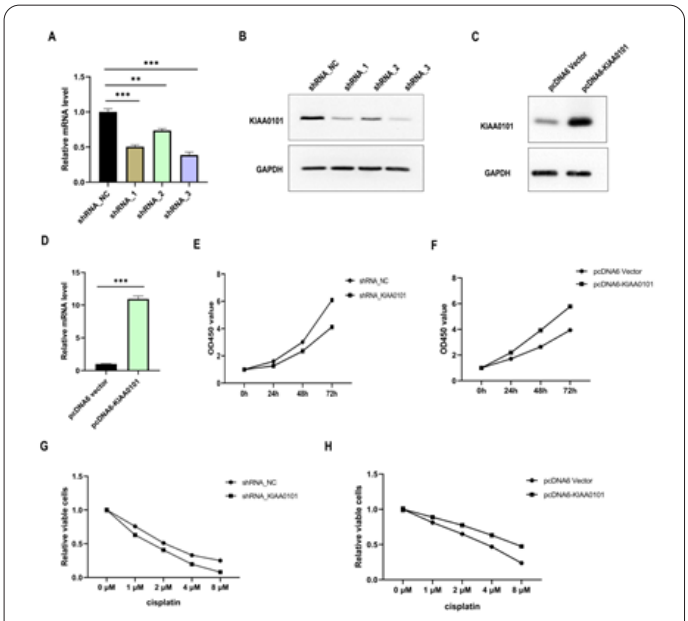

Figure 2. KIAA0101 enhanced proliferation and cisplatin sensitivity of lung cancer cells. The mRNA (A) and protein (B) levels of KIAA0101 were detected by RT-qPCR and WB after transfection of A549 cells with KIAA0101 shRNA for 72 hours. KIAA0101 was overexpressed in A549 cells, and the protein (C) and mRNA (D) levels of KIAA0101 were detected by WB and RT-qPCR. Effect of knockdown (E) or overexpression (F) of KIAA0101 on cell proliferation of A549 cells; Effect of cisplatin on the sensitivity of A549 cells knockdown (G) or overexpressing(H) KIAA0101.

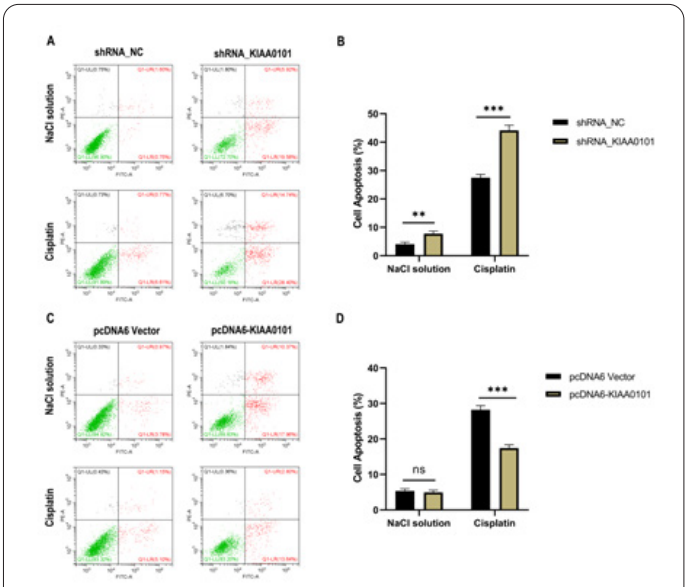

Figure 3. Effect of KIAA0101 on cisplatin-induced apoptosis of A549 cells. Flow cytometry was used to detect cisplatin-induced apoptosis induced by knockdown (A, B) or overexpression (C, D) in A549.

KIAA0101 regulated the activation of the related apoptosis pathway

To detect the influence of KIAA0101 on the apoptosis signaling pathway, western blotting analysis was conducted. In NC cells, cisplatin-induced significant activation of the apoptosis signaling pathway, featured an increased level of p-p53, c-caspase 3, bax, and a reduced level of bcl2 (Fig. 4A-G). It was found that knockdown of the KIAA0101 induced stronger activation of these factors in apoptosis, including elevation of bax, c-caspase-3, p-p53, and KIAA0101 knockdown reduced the level of bcl2 (Fig. 4A-G). These findings revealed that KIAA0101 is related to a cell apoptosis signaling pathway in the cisplatin-induced cell death.

Blockage of the p53 signaling pathway rescued the influence of KIAA0101 on cisplatin

P53 is a master factor that orchestrates the cell apoptosis signaling pathway. Then we established p53 knockdown cells in NC and KIAA0101 shRNA transfected A549 cells (Fig. 5A, B). Our data showed that in p53 and KIAA0101 knockdown cells and augment of cisplatin on bax and c-caspase 3 was significantly suppressed, indicating that KIAA0101 regulates cell apoptosis pathway is p53 dependent (Fig. 5C). Then using apoptosis assay, we found that KIAA0101 knockdown didn't further increase the apoptosis rate (Fig. 5D). This confirmed and is consistent with the signaling pathway assay.

Discussion

In this study, we first revealed that cell proliferation-

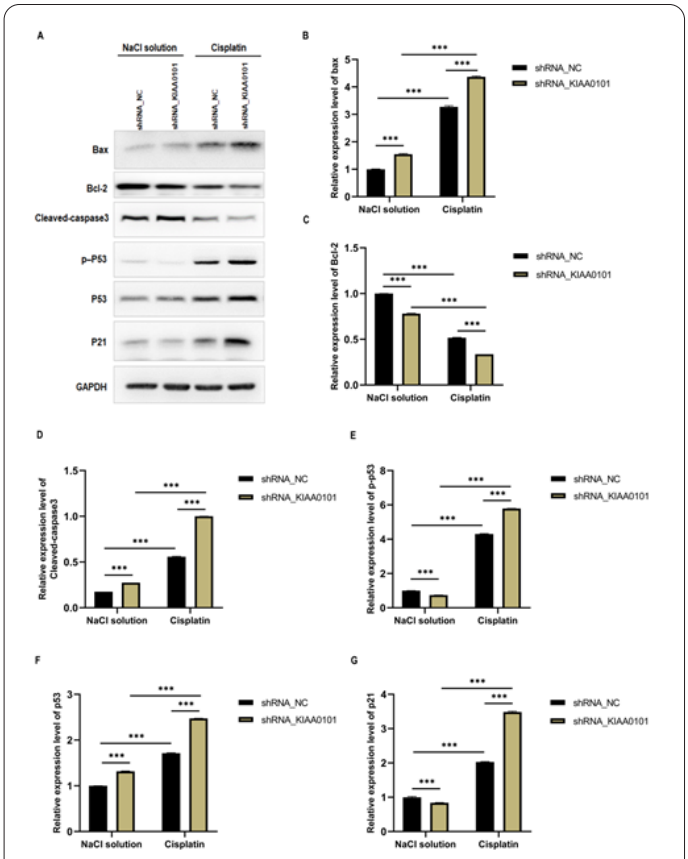

Figure 4. KIAA0101 is involved in the regulation of the apoptosis signaling pathway. A549 cells transfected with KIAA0101 knockout and control plasmids were treated with cisplatin, and the protein levels of apoptosis signaling pathway were detected by WB (A); Image J 6.0 was used for gray analysis of WB results and histogram was drawn (B-G) ($p \leq 0.05$).

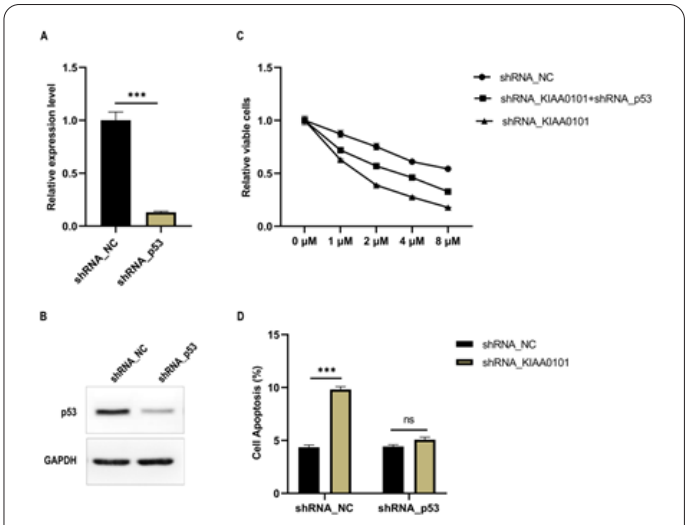

Figure 5. P53 involved in the effect of KIAA0101 on cisplatin. After transfection with p53 knockdown plasmid, RT-qPCR and WB were used to detect the interference effect of shRNA on p53 mRNA (A) and protein (B) levels. A549 cells were co-transformed with p53 and KIAA0101 knockdown plasmids and treated with cisplatin. Cell survival efficiency was detected by CCK8 assay (C), and cell apoptosis was detected by flow cytometry (D).

related protein KIAA0101 was involved in cisplatin resistance of lung cancer cells. KIAA0101 was found to be elevated in lung cancer tissues, compared with normal tissues. Knockdown of KIAA0101 significantly suppressed cell proliferation and enhanced cisplatin-induced apoptosis of lung cancer cells. In contrast, overexpression of KIAA0101 promoted cell proliferation and escape from apoptosis after cisplatin treatment. Cell apoptosis pathway was also increased in KIAA0101 knockdown cells than NC group, which was related to a p53-related mechanism. Our study provides a novel potential target for overcoming cisplatin resistance in lung cancer.

As a cell proliferation-related factor, KIAA0101 was found to be upregulated and functions as an oncogene in many types of cancers. In adrenal cancer, KIAA0101 was found to be upregulated and promotes cell proliferation and tumor growth. KIAA0101 was also upregulated in the metastatic epithelial ovarian cancer tissues and enhanced the migration as well as chemoresistance. In esophageal cancer patients, KIAA0101 was also increased and correlated with poor prognostics and KIAA0101 high tissues are resistant to cisplatin treatment. Mechanistically, KIAA0101 was a target of transcriptional factor FoxM1, which accounts for the upregulation of KIAA0101 in hepatocellular carcinoma. We and several studies revealed that KIAA0101 was elevated in lung cancer tissues, and correlated with poor outcomes in cancer patients. The increase of KIAA0101 could also be as a potential biomarker for lung cancer or cisplatin resistance.

Cellular experiments showed that KIAA0101 was strongly related to cell proliferation and cisplatin-induced apoptosis in lung cancer cells. Our findings in lung cancer are also supported in studies of other types of cancers. Jin et al reported that KIAA0101 predicts poor progress in high-grade serous ovarian cancer patients, and also regulates cisplatin-related apoptosis and autophagy through the PI3K/AKT/mTOR signaling pathway. KIAA0101 also interacts with BRCA1 to regulate centrosome formation in breast cancer. Cisplatin often induced cell apoptosis in a p53-bax-caspase 3 signaling pathway. We observed more activation of the cell apoptosis pathway in KIAA0101 knockdown cells, while less activation in KIAA0101 overexpression cells. This data showed that KIAA0101 suppresses cisplatin-induced cell apoptosis, through inhibiting apoptosis signaling pathway. In a study of hepatocellular carcinoma, KIAA0101 was related to exerting an anti-apoptosis role in the doxorubicin-induced cell apoptosis and p53 signaling pathway. Our findings provide a novel mechanism that knockdown of KIAA0101 increased pro-apoptosis factor bax and cleaved caspase 3, while suppressing bcl2, an anti-apoptotic factor. These data showed that targeting KIAA0101 could be used a potential strategy for treating lung cancer.

Our study showed that combined therapy through inhibiting KIAA0101 and cisplatin treatment could be regarded as novel combinations for novel cancer therapy methods. To the current knowledge, siRNA or lentivirus-based shRNA delivery is often used to target a gene in solid tumors. These kinds of gene therapy should be performed in a precise way, while the effects of KIAA0101 on normal cells and tissues should be investigated. Small molecular chemical inhibitors are also a choice to screen the potential inhibitors for KIAA0101, which will provide novel chemical drugs for combined therapy with cisplatin. Recently, CRISPR cas9-based gene editing is drawing more and more attention, and specific depletion of KIAA0101 in lung cancer cells also represents a very potent strategy. More experiments are still required to proceed with the

clinical transformation of targeting KIAA0101.

In conclusion, our study uncovered a novel cisplatin resistance-related gene, KIAA0101. Based on its biological feature, KIAA0101 was related to cell proliferation and apoptosis induced by cisplatin. Knockdown of KIAA0101 also augmented the apoptosis signaling pathway activated by cisplatin in a p53-dependent manner. Our findings provide a novel target for combined therapy of targeting KIAA0101 together with cisplatin treatments.

Conflicts of interest

The authors have no conflict of interest to disclose.

Acknowledgements

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Data availability statement

The data sets used or analyzed during the current study are available from the corresponding author.

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