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ORIGINAL RESEARCH

Long Non-Coding RNA SLC25A21-AS1 Promotes Multidrug Resistance in Nasopharyngeal Carcinoma by Regulating miR-324-3p/IL-6 Axis

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Xiaoqin Wang[1]
Chunhui Wang[1]
Hong Xu[1]
Hong Xie[2]

[1]Department of Otolaryngology, Liangxiang Hospital, Capital Medical University, Beijing 102401, People's Republic of China; [2]Department of Otolaryngology Head and Neck Surgery, Beijing Shijitan Hospital, Capital Medical University, Beijing 100038, People's Republic of China

Background: Nasopharyngeal carcinoma (NPC), one of the most common types of head and neck tumor, occurred in the epithelial lining of the nasopharynx and is mainly prevalent in Southeast Asia and Southern China. However, the molecular mechanisms of NPC multidrug resistance still remained largely unclear.

Methods: The qRT-PCR assay was performed to examine SLC25A21-AS1, miR-324-3p and IL-6 expression in NPC tissues and cell. The CCK8 assay and colony formation assay were used to detect cell growth. In addition, CCK8 assay was performed to detect IC_{50} values of different drugs in NPC cell.

Results: In this study, we found that SLC25A21-AS1 expression was increased in NPC tissues and cell line, and knockdown of SLC25A21-AS1 inhibited cell growth and MDR in NPC cell. Moreover, SLC25A21-AS1 acted as a ceRNA for miR-324-3p and facilitates NPC cell growth and MDR by regulating the miR-324-3p/IL-6 axis.

Conclusion: Our findings demonstrated the role of SLC25A21-AS1/miR-324-3p/IL-6 axis in cell growth and MDR in NPC, which might be a potential prognostic and diagnostic marker in NPC patients and provide new insight into the molecular mechanism of MDR in NPC chemotherapy.

Keywords: SLC25A21-AS1, cell growth, MDR, miR-324-3p, IL-6

Introduction

Nasopharyngeal carcinoma (NPC), one of the most common types of head and neck tumor, occurred in the epithelial lining of the nasopharynx and is mainly prevalent in Southeast Asia and Southern China.[1,2] Over the past decades, chemotherapy as a primary method for the treatment of NPC has been markedly improving, but prognosis still remains poor due to multidrug resistance (MDR).[2,3] Thus, further study for the molecular mechanisms of NPC multidrug resistance is urgently required.

Long non-coding RNAs (lncRNAs) are endogenous and long non-coding RNA molecules (~200nt) that regulate gene expression by targeting miRNA or mRNA posttranscriptionally.[4–7] Increasing studies have revealed lncRNAs played crucial roles in tumorigenesis, metastasis and MDR. For example, lncRNA DANCR promotes tumor progression and cancer stemness features in osteosarcoma by upregulating AXL via miR-33a-5p inhibition.[8] LncRNA-CCAT1 promotes migration, invasion, and EMT in intrahepatic cholangiocarcinoma through suppressing miR-152.[9] LncRNA-UCA1 enhances cell proliferation and 5-fluorouracil resistance

Correspondence: Xiaoqin Wang
Tel +86 010-81356147
Email yinsonglou002@163.com

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in colorectal cancer by inhibiting miR-204-5p.[10] In addition, lncRNAs could be also considered as prognostic or diagnostic biomarkers regarding their effects in clinical characteristics of tumor prognosis. For example, lncRNA BC200 is a potential predictive marker of poor prognosis in esophageal squamous cell carcinoma patients.[11] However, the molecular mechanisms of NPC multidrug resistance still remained largely unclear.

Mechanically, the effects of lncRNAs mainly involve miRNA binding and regulate target gene expression by sponging miRNA. For example, lncRNA MALAT1 promotes tumor growth and metastasis by targeting miR-124/foxq1 in bladder transitional cell carcinoma.[12] LncRNA XIST/miR-34a axis modulates the cell proliferation and tumor growth of thyroid cancer through MET-PI3K-AKT signaling.[13] LncRNA SPRY4-IT1 sponges miR-101-3p to promote proliferation and metastasis of bladder cancer cells through up-regulating EZH2.[14] Thus, analysis of the lncRNA-miRNA-mRNA network has crucially great significance.

In this study, we firstly identified lncRNA SLC25A21-AS1 were upregulated in NPC tissues and cell. In addition, we also found SLC25A21-AS1 promotes NPC cell proliferation and MDR by regulating the miR-324-3p/IL-6 axis.

Materials and Methods

Patients and Specimens

Seventy-six pairs of NPC samples and adjacent normal tissues were collected from Liangxiang Hospital of Capital Medical University. None of the patients had received chemotherapy or radiotherapy before the surgery. This study was approved by the Institutional Research Ethics Committee of Liangxiang Hospital of Capital Medical University. Written informed consent was attained from all subjects, and all methods were performed in accordance with the Declaration of Helsinki.

Cell Culture and Transfection

The human nasopharyngeal epithelial cell line NP69 and human NPC cell lines SUNE-1, CNE-1, CNE-2, HNE-1, C666-1 and HONE-1 were purchased from the Chinese Academy of Sciences Cell Bank. SUNE-1, CNE-1, CNE-2, HNE-1, C666-1 and HONE-1 cell were culture in RPMI-1640 medium (Gibco, Grand Island, NY, USA) supplemented with 10% FBS (Gibco, Grand Island, NY, USA) and 1% penicillin-streptomycin sulfate (Thermo Fisher Scientific). NP69 cell was maintained in keratinocyte/serum-free medium (Invitrogen, GrandIsland, NY, USA) supplemented with bovine pituitary extract. All cultures were maintained in a 37°C incubator supplemented with 5% CO2. To knock down SLC25A21-AS1, the cells were infected with Lipofectamine 3000 (Gibco). SLC25A21-AS1 shRNA were 5′-GACGCCGAGGCAACTTTACTT-3′.

CCK8 Assay and Colony Formation Assay

CCK8 assay was carried out following the manufacturer's instructions.[15,16] The absorbance was detected spectrophotometrically at 450 nm. For cell colony formation assay, 2000 cells were seeded in 6-well plate and cultured in RPMI-1640 medium (Gibco, Grand Island, NY, USA) supplemented with 10% FBS (Gibco, Grand Island, NY, USA). After 14 Days, the cell colonies were stained with crystal violet and counted.

Animal Experiments

NPC cells were injected subcutaneously into the flanks of nude mice according to the guidelines of the Laboratory Animal Centre. An evident tumor (80–100 mm^3) was observed after cell injection, and mice were injected intraperitoneally 15 μg/g cisplatin once in every 7 days. The tumor volume was measured every 1 week and was calculated according to the following formula: 1/2 × length × $width^2$, and the tumor weight was calculated after 4 weeks. All experiment protocols were approved by the Institutional Research Ethics Committee of Liangxiang Hospital of Capital Medical University, and the animals were cared for in agreement with Institutional ethics guidelines.

Experiments of Separating Nuclei from Cytoplasm

MirVana™ PARIS™ Kits (Ambion, Shanghai) was used and strictly operated according to the manufacture's instructions.

Luciferase Reporter Assay

The SLC25A21-AS1 WT, SLC25A21-AS1 Mut, IL-6 WT or IL-6 Mut were co-transfected with miR-324-3p mimics, miR-324-3p inhibitor or miR-NC into NPC cells. The relative luciferase activity was detected by the Dual-Glo Luciferase Assay System (Promega) referring to the instructions of the manufacturer.

RNA Immunoprecipitation (RIP) Assay

RIP assay was exercised by Imprint RNA immunoprecipitation kit (Sigma-Aldrich) according to the manufacture's instructions. The relative enrichment of SLC25A21-AS1 and miR-324-3p was detected by qRT-PCR analysis.

Quantitative Real-Time RT-PCR (qRT-PCR)

Total RNA was extracted from cells or tissues using the TRIzol kit (Invitrogen, Grand Island, NY, USA) following the manufacture's instructions. Quantitative real-time RT-PCR (qRT-PCR) analysis was used to examine the lncRNA, miRNA and mRNA expressions via using SYBR green kit (TaKaRa, Dalian, China) on the Light Cycler 480 (Roche, Switzerland) in accordance with the manufacturer's instructions. The primers used for qPCR include: SLC25A21-AS1 forward, 5′-AGCACTGCTCCG GGAGCGCTG-3′ and reverse, 5′-TAGTGCGCGAGGCT TCTCGGC-3′; GAPDH forward, 5′-AGCCACATCGCTC AGACAC-3′, and reverse, 5′-GCCCAATACGACCAAAT CC-3′. MiR-324-3p forward, 5′-ACACTCCAGCTGGGA CTGCCCCAGGTGC-3′ and reverse, 5′-TGGTGTCGTG GAGTCG-3′. IL-6 forward, 5′-GGCCCTTGCTTTCTC TTCG-3′ and 5′-ATAATAAAGTTTTGATTATGT-3′.

ELISA

IL-6 ELISA kits were purchased from Sigma-Aldrich (St. Louis, MO, USA), and experiments were performed according to the manufacturer's instructions.

Statistical Analysis

Differences among groups were analyzed by ANOVA or Student's *t*-test using (GraphPad Software Inc., La Jolla, CA) and the SPSS 23.0 software (SPSS, Chicago, IL, USA). Correlation was analyzed by a Pearson's test after normality tests. All data are expressed as the means ± SD. $P<0.05$ was defined as a statistically significant difference.

Result

SLC25A21-AS1 Expression Was Increased in NPC Tissues and Cell Lines

Using the bioinformatics tool GEO2R (https://www.ncbi.nlm.nih.gov/geo/geo2r/?acc=GSE95166), we analyzed GEO dataset (GSE95166) for lncRNAs from NPC tissues (n = 4). The results showed SLC25A21-AS1 expression was upregulated in NPC tissues (Figure 1A). Subsequently, we examined SLC25A21-AS1 expression in 76 pairs of NPC samples and adjacent normal tissues. The results showed SLC25A21-AS1 expression was increased in NPC tissues compared to adjacent normal tissues (Figure 1B). In addition, 76 NPC patients were split into high and low SLC25A21-AS1 expression groups according to the median value, and higher SLC25A21-AS1 expression implied a lower survival rate in NPC patients (Figure 1C). Moreover, high SLC25A21-AS1 expression was associated with large T stage, tumor size, and lymph node metastasis (Table 1). Correspondingly, we also found SLC25A21-AS1 expression was increased in NPC cells compared with human nasopharyngeal epithelial cell line NP69 (Figure 1D). Thus, these results revealed overexpression of SLC25A21-AS1 might be critical to NPC progression.

Knockdown of SLC25A21-AS1 Inhibited Cell Growth and MDR in NPC Cell

To explore the effect of SLC25A21-AS1 on NPC cell growth, CNE-1 and HNE-1 cells were transfected with sh-NC or sh-SLC25A21-AS1 (sh-SA). The qRT-PCR assay showed SLC25A21-AS1 expression in CNE-1/sh-SA and HNE-1/sh-SA cells were downregulated compared with CNE-1/sh-NC and HNE-1/sh-NC cells (Figure 2A). In addition, CCK8 assay (Figure 2B) and colony formation assay (Figure 2C) revealed cell growth in CNE-1/sh-SA, and HNE-1/sh-SA cells were inhibited compared with CNE-1/sh-NC and HNE-1/sh-NC cells. Notably, animal experiments showed silencing SLC25A21-AS1 suppressed tumor size in vivo (Figure 2D), and the tumor weight of the sh-SA group was lighter than the sh-NC group (Figure 2E). Furtherly, we found SLC25A21-AS1 expression was upregulated in cisplatin-resistant NPC cells (SUNE-1/CDDP, CNE-1/CDDP, CNE-2/CDDP, HNE-1/CDDP, C666-1/CDDP and HONE-1/CDDP) (Figure 2F) compare to NPC cells. Notably, the SLC25A21-AS1 expression in serum was increased in NPC patients after cisplatin and 5-FU combined chemotherapy compared with before cisplatin and 5-FU combined chemotherapy (Figure 2G). Moreover, CCK8 assay revealed that IC_{50} values of different drugs in CNE-1/sh-SA and HNE-1/sh-SA cells were significantly reduced compared to CNE-1/sh-NC and HNE-1/sh-NC cells (Figure 2H), and animal experiments showed the sh-SA group with cisplatin treatment more effectively suppressed tumor size (Figure 2D) and reduced tumor weight (Figure 2E) compared to the sh-NC group with cisplatin treatment. Therefore, these results

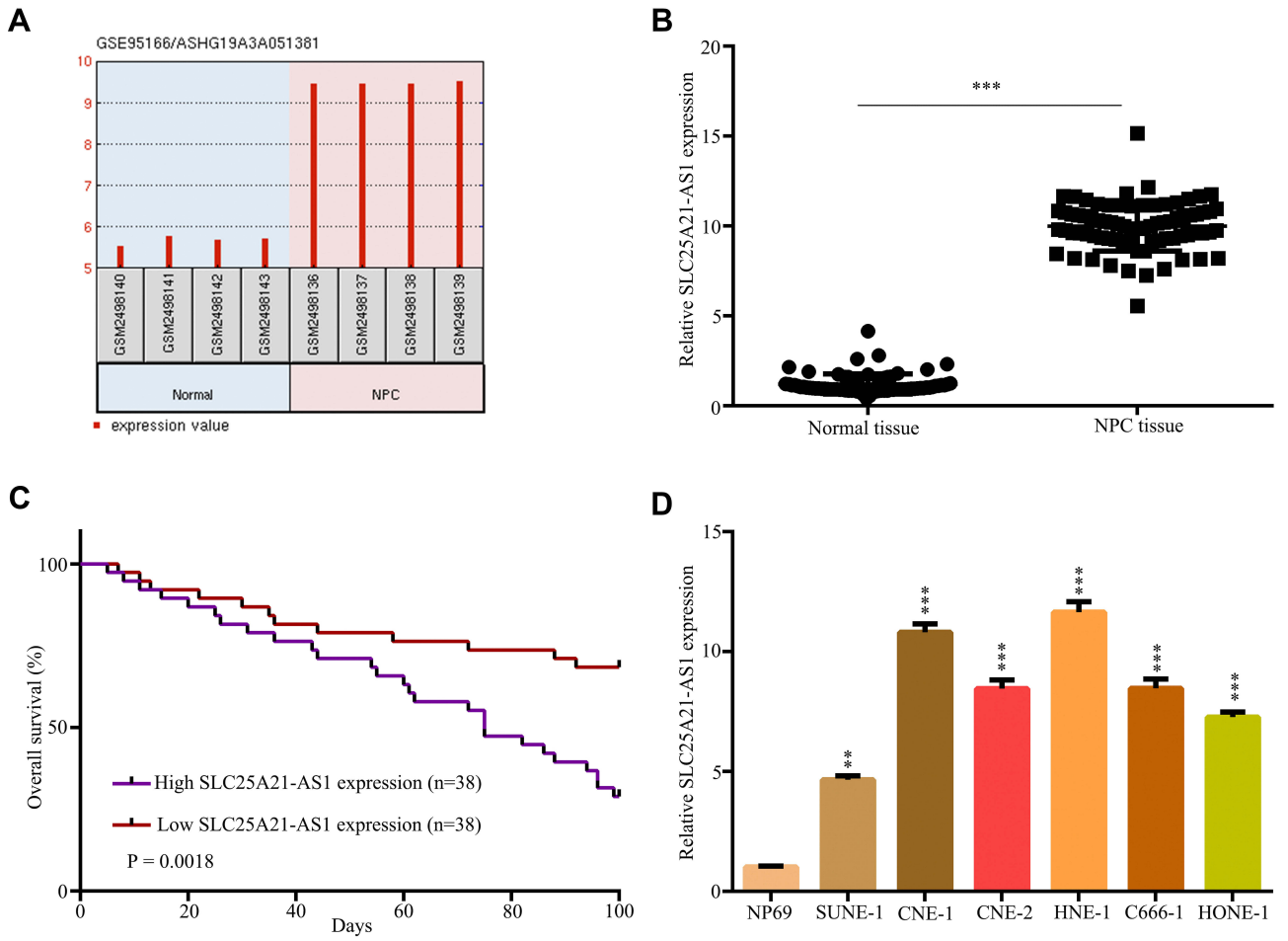


Figure 1 SLC25A21-AS1 expression was increased in NPC tissues and cell lines. (**A**) GEO dataset (GSE95166) showed that SLC25A21-AS1 was remarkably upregulated in NPC tissues compared to normal tissues. (**B**) SLC25A21-AS1 was significantly increased in NPC tissues compared to normal tissues (n=76). (**C**) Survival rate was detected by Kaplan-Meier analysis in NPC patients. (**D**) SLC25A21-AS1 was remarkably upregulated in NPC cell compared to NP69 cell. **P < 0.01, ***P < 0.001. Means ± SD are shown.

revealed knockdown of SLC25A21-AS1 inhibited NPC cell growth and MDR in vitro and in vivo.

SLC25A21-AS1 Acts as a ceRNA for miR-324-3p to Promote Cell Growth and MDR in NPC

Increasing studies pointed out lncRNAs might function as a ceRNA or a molecular sponge in regulating the biological functions of miRNA. To explore whether lncRNA interacted directly with miRNA to regulate the expression of miRNA's targets in NPC, the position distribution of SLC25A21-AS1 in CNE-1 and HNE-1 cells was first examined. The results revealed that SLC25A21-AS1 was mostly located in the cytoplasm of CNE-1 and HNE-1 cell (Figure 3A). To identify miRNAs interacted with SLC25A21-AS1, we analyzed the overlap from the results of miRDB, starbase and DIANA tool to predict potential binding sites. The results revealed SLC25A21-AS1 may bind to miR-324-3p (Figure 3B), and luciferase reporter assay had further verified their complementary combinations (Figure 3C), suggested miR-324-3p bounded to and inhibited SLC25A21-AS1 activity. In addition, the qRT-PCR assay showed RIP assay showed the direct binding between SLC25A21-AS1 and miR-324-3p (Figure 3D), and miR-324-3p expression in CNE-1/sh-SA and HNE-1/sh-SA cells were significantly increased compared to CNE-1/sh-NC and HNE-1/sh-NC cells (Figure 3E). Subsequently, we further detected miR-324-3p expression in NPC tissues. The results showed miR-324-3p expression was decreased in NPC tissues compared to adjacent normal tissues (Figure 3F), and Pearson correlation analysis revealed SLC25A21-AS1 expression was inversely correlated with miR-324-3p in NPC tissues (Figure 3G).

To further explore the regulatory relationship between SLC25A21-AS1 and miR-324-3p in NPC cell, CNE-1 and

Table 1 Correlation Between SLC25A21-AS1 Expression and Clinicopathological Characteristics in NPC

Variables	SLC25A21-AS1 Expression		p
	Low	High	
Sex			0.765
Male	21	22	
Female	17	16	
Age			0.622
<45	19	17	
≧45	19	21	
T stage			<0.05
T3 + T4	13	26	
T1 + T2	25	12	
Tumor size			<0.05
≧5	11	30	
<5	27	8	
Lymph node metastasis			<0.05
Yes	15	26	
No	23	12	

HNE-1 cell were transfected with sh-SA and miR-324-3p mimic or inhibitor. The qRT-PCR showed miR-324-3p expression was promoted in transfected with miR-324-3p mimic, while miR-324-3p expression was inhibited in transfected with miR-324-3p inhibitor (Figure 3H). Notably, the miR-324-3p expression in transfected with sh-SA and miR-324-3p inhibitor was higher than transfected with miR-324-3p inhibitor alone. In addition, CCK8 assay showed cell growth was suppressed in transfected with miR-324-3p mimic, while cell growth was promoted in transfected with miR-324-3p inhibitor (Figure 3I). Moreover, IC_{50} values of different drugs were significantly reduced in transfected with miR-324-3p mimic, while IC_{50} values of different drugs were increased in transfected with miR-324-3p inhibitor (Figure 3J). Hence, SLC25A21-AS1 acts as a ceRNA for miR-324-3p to promote cell growth and MDR in NPC.

SLC25A21-AS1 Facilitates NPC Cell Growth and MDR by Regulating miR-324-3p/IL-6 Axis

To identify mRNAs interacted with miR-324-3p, we analyzed the overlap from the results of starbase and TargetScan to predict potential binding sites. The results revealed miR-324-3p may bind to IL-6 3′ UTR (Figure 4A), and luciferase reporter assay had further verified their complementary combinations (Figure 4B), suggested miR-324-3p bounded to IL-6 3′ UTR and inhibited IL-6 expression. In addition, qRT-PCR assay and ELISA assay revealed IL-6 expression was inhibited in transfected with miR-324-3p mimic, while IL-6 expression was promoted in transfected with miR-324-3p inhibitor (Figure 4C and D). Subsequently, we further detected IL-6 expression in NPC tissues. The results showed IL-6 expression was increased in NPC tissues compared to adjacent normal tissues (Figure 4E), and Pearson correlation analysis revealed IL-6 expression was inversely correlated with miR-324-3p in NPC tissues (Figure 4F). Notably, SLC25A21-AS1 expression is positively correlated with IL-6 (Figure 4G). Moreover, CNE-1/sh-SA and 285HNE-1/sh-SA cells were transfected with the miR-324-3p inhibitor and si-IL-6, and RT-PCR and ELISA assay demonstrated the IL-6 expression with transfected miR-324-3p inhibitor was increased compared to transfected miR-NC and IL-6 expression with transfected si-IL-6 was inhibited compared to transfected si-NC (Figure 4H and I). Knockdown of IL-6 suppressed cell growth and reduced IC_{50} values of different drugs, and transfected miR-324-3p inhibitor promoted cell growth and increased IC_{50} values of different drugs in transfected si-IL-6 (Figure 4J and K). Therefore, SLC25A21-AS1 facilitates NPC cell growth and MDR by regulating the miR-324-3p/IL-6 axis.

Discussion

Long non-coding RNAs (lncRNAs) are endogenous and long non-coding RNA molecules (~200nt) that regulate gene expression by targeting miRNA or mRNA posttranscriptionally. Increasing studies have revealed lncRNA played crucial roles in tumorigenesis, metastasis and MDR.[8,17,18] Notably, earlier reports also indicated that lncRNA is associated with the tumorigenesis, metastasis and MDR of NPC. For example, lncRNA ANRIL is upregulated in nasopharyngeal carcinoma and promotes the cancer progression via increasing proliferation, reprograming cell glucose metabolism and inducing side-population stem-like cancer cells.[19] LncRNA NEAT1/let-7a-5p axis regulates the cisplatin resistance in nasopharyngeal carcinoma by targeting Rsf-1 and modulating the Ras-MAPK pathway.[20] LncRNA UCA1 affects epithelial–mesenchymal transition, invasion, migration and apoptosis of nasopharyngeal carcinoma cells.[21] In this study, SLC25A21 was first identified in NPC by using the bioinformatics tool GEO2R and was increased in NPC tissues. Moreover, knockdown of SLC25A21-

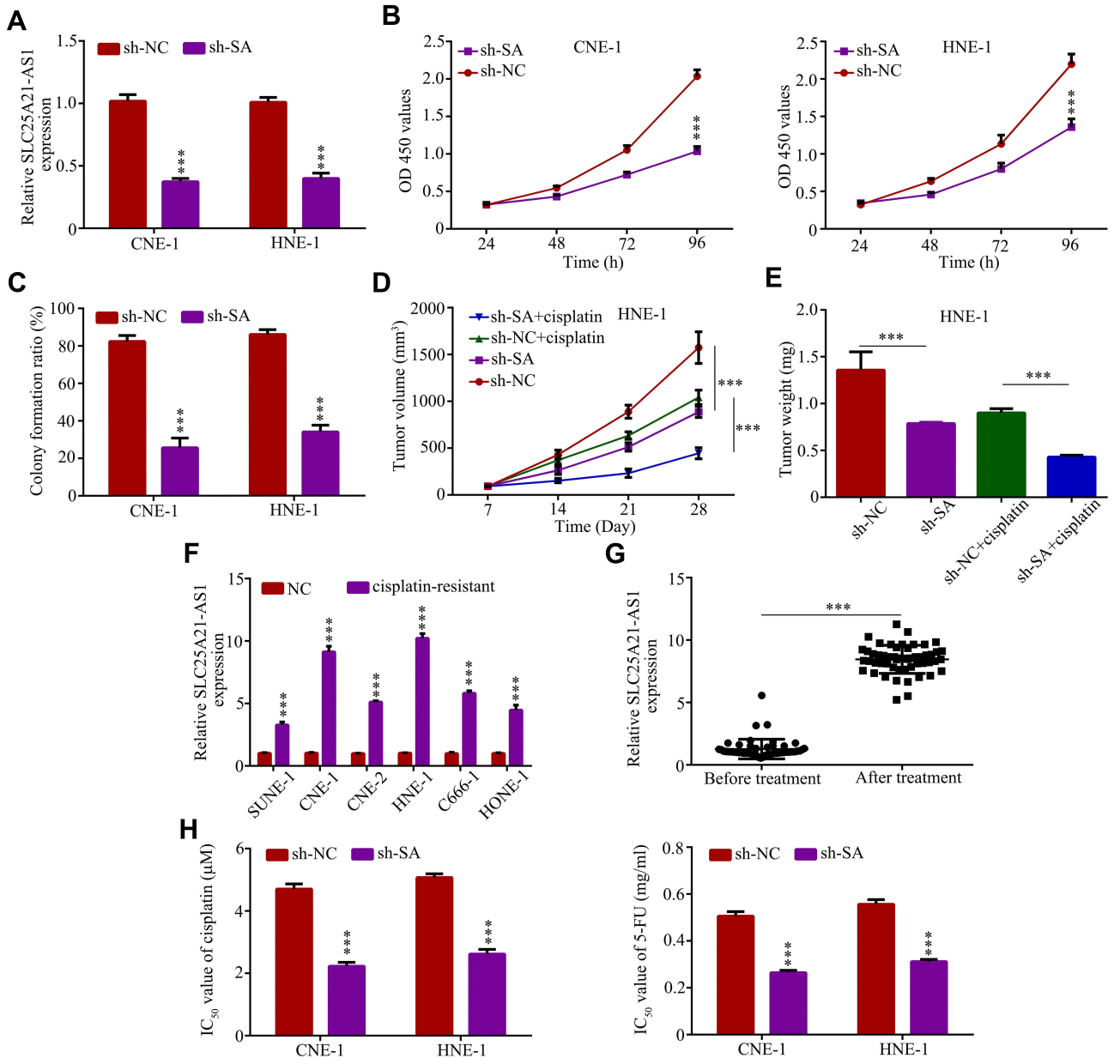


Figure 2 Knockdown of SLC25A21-AS1 inhibited cell growth and MDR in NPC cell. (**A**). Relative SLC25A21-AS1 expression was detected after transfection with control. Cell growth (**B**) and colony formation (**C**) were detected after transfection of SLC25A21-AS1 with control. Tumor volume (**D**) and tumor weight (**E**) were detected in nude mice. (**F**) SLC25A21-AS1 expression was detected in cisplatin-resistant NPC cells. (**G**) SLC25A21-AS1 expression in serum was detected before treatment and after treatment. (**H**) IC_{50} values of different drugs were examined by CCK8 assay. ***P < 0.001. Means ± SD are shown.

AS1 inhibited cell growth and reduced IC_{50} values of different drugs, suggested SLC25A21-AS1 might be critical to NPC progression.

The effects of lncRNA mainly involved miRNA binding, and regulated target gene expression by sponging miRNA. Early study pointed out miR-324-3p suppresses migration and invasion by targeting WNT2B in nasopharyngeal carcinoma.[22] In addition, SLC25A21-AS1 was found to bind to miR-324-3p by using miRDB, starbase and DIANA tool, and SLC25A21-AS1 expression was inversely correlated with miR-324-3p in NPC tissues. Thus, SLC25A21-AS1 acts as a ceRNA for miR-324-3p to promote cell growth and MDR in NPC. Notably, IL-6 was first identified as a direct target for miR-324-3p. Some studies indicated upregulation of IL-6 expression was associated with cell growth and MDR. For example, overexpression of IL-6 can contribute to tumor growth by altered promoter methylation and gene expression in human cholangiocarcinoma.[23] IL-6 signaling contributes to cisplatin resistance in non-small cell lung cancer via

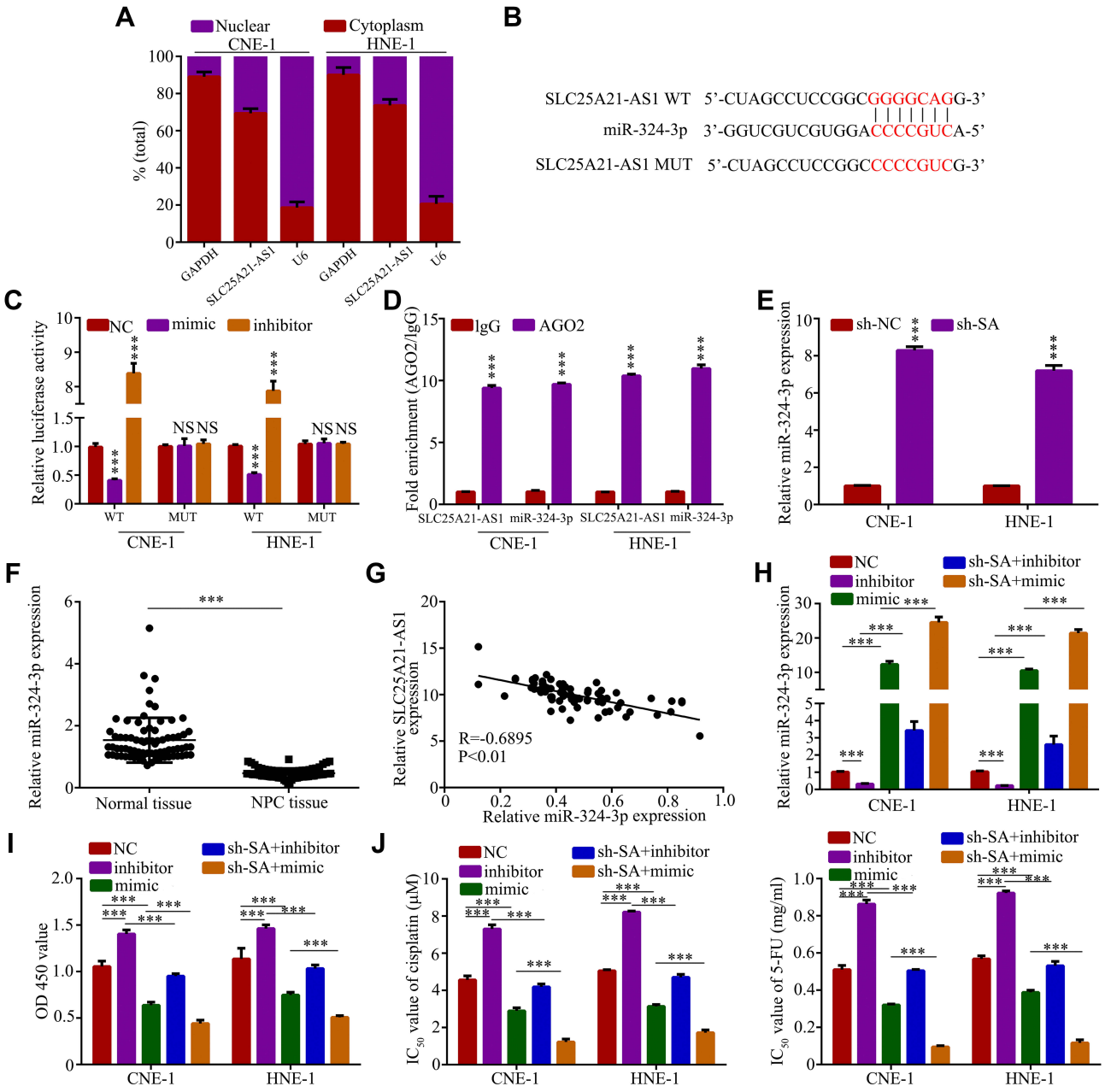


Figure 3 SLC25A21-AS1 acts as a ceRNA for miR-324-3p to promote cell growth and MDR in NPC. (**A**) Subcellular location of SLC25A21-AS1 was detected in NPC cell. (**B**) Sequence alignment of miR-324-3p with the putative binding sites within the wild-type or mutant regions of SLC25A21-AS1. (**C**) Luciferase reporter assay verified complementary combinations between SLC25A21-AS1 and miR-324-3p. (**D**) RIP and RT-PCR assays are performed to detect the enrichment of SLC25A21-AS1 and miR-324-3p. (**E**) MiR-324-3p expression was detected after transfection of SLC25A21 with control. (**F**) MiR-324-3p expression was decreased in NPC tissue compared to normal tissue. (**G**) SLC25A21-AS1 expression was inversely correlated with miR-324-3p in NPC tissues. (**H**) MiR-324-3p expression was detected after transfection of miR-324-3p mimic or miR-324-3inhibitor. (**I**) Cell growth was detected after transfection of miR-324-3p mimic or miR-324-3inhibitor. (**J**) IC_{50} values of different drugs were detected after transfection of miR-324-3p mimic or miR-324-3 inhibitor. ***P < 0.001, ^{NS}P > 0.05. Means ± SD are shown.

Abbreviations: sh-SA, sh-SLC25A21-AS1; mimic, miR-324-3p mimic; inhibitor, miR-324-3 inhibitor.

the up-regulation of anti-apoptotic and DNA repair associated molecules.[24] Enhanced IL-6/IL-6R signaling promotes growth and malignant properties in EBV-infected premalignant and cancerous nasopharyngeal epithelial cells.[25] In this study, we found that IL-6 was remarkably increased in NPC tissues. In addition, IL-6 expression was inversely correlated with miR-324-3p in NPC tissues, and SLC25A21-AS1 expression is positively correlated with IL-6. Moreover, upregulated IL-6 expression promoted NPC cell growth and MDR, while downregulation of IL-6 inhibited it. Thus, SLC25A21-AS1 facilitates NPC cell growth and MDR by regulating the miR-324-3p/IL-6 axis.

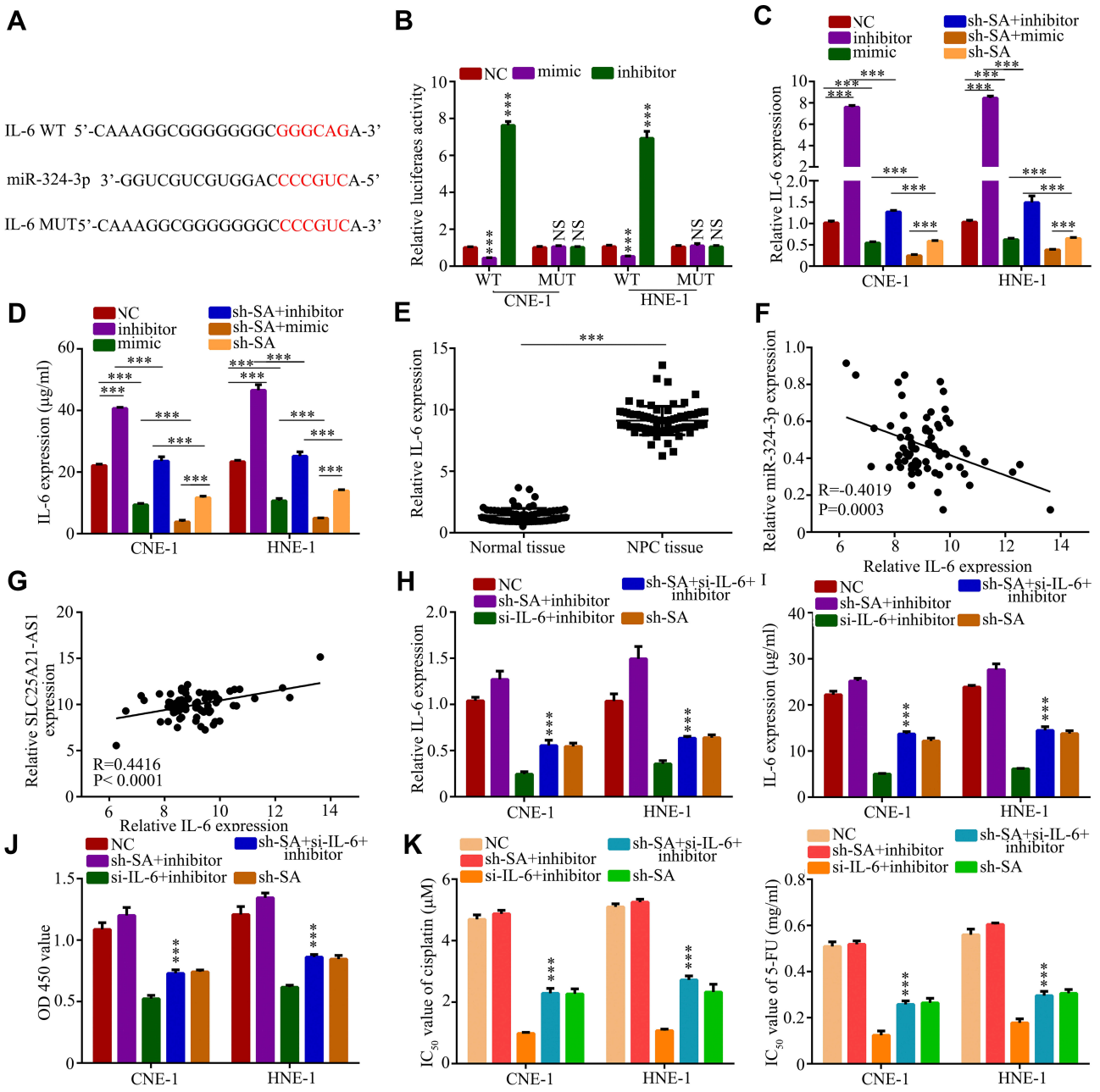


Figure 4 SLC25A21-AS1 facilitates NPC cell growth and MDR by regulating miR-324-3p/IL-6 axis. (**A**) Sequence alignment of miR-324-3p with the putative binding sites within the wild-type or mutant regions of IL-6. (**B**) Luciferase reporter assay verified complementary combinations between miR-324-3p and IL-6. IL-6 expression was detected by RT-PCR (**C**) and Elasi assay (**D**). (**E**) IL-6 expression was detected in NPC tissue compared to normal tissue. (**F**) IL-6 expression was inversely correlated with miR-324-3p in NPC tissues. (**G**). SLC25A21-AS1 expression is positively correlated with IL-6. H. IL-6 expression was detected by RT-PCR (**H**) and Elasi assay (**I**). (**J**) Cell growth was examined by CCK8 assay. (**K**) IC_{50} values of different drugs were detected by CCK8 assay. ***P < 0.001, ^{NS}P > 0.05. Means ± SD are shown.
Abbreviations: sh-SA, sh-SLC25A21-AS1; mimic, miR-324-3p mimic; inhibitor, miR-324-3 inhibitor.

In summary, we first found that SLC25A21-AS1 was increased in NPC tissues and cells. Higher SLC25A21-AS1 expression was correlated with poor prognosis in NPC patients. Knockdown of SLC25A21-AS1 exhibited tumor-suppressive roles via suppressing NPC cell growth in vitro and in vivo. Moreover, SLC25A21-AS1 promotes cell growth and MDR in NPC by functioning as a molecular sponge of miR-324-3p and subsequently increasing IL-6 expression. Therefore, our findings demonstrated the role of SLC25A21-AS1/miR-324-3p/IL-6 axis in cell growth and MDR of NPC, which might be a potential prognostic and diagnostic marker in NPC patients and provides new insight into the molecular mechanism of MDR in NPC chemotherapy.

Disclosure

The authors declare no conflict of interest.

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