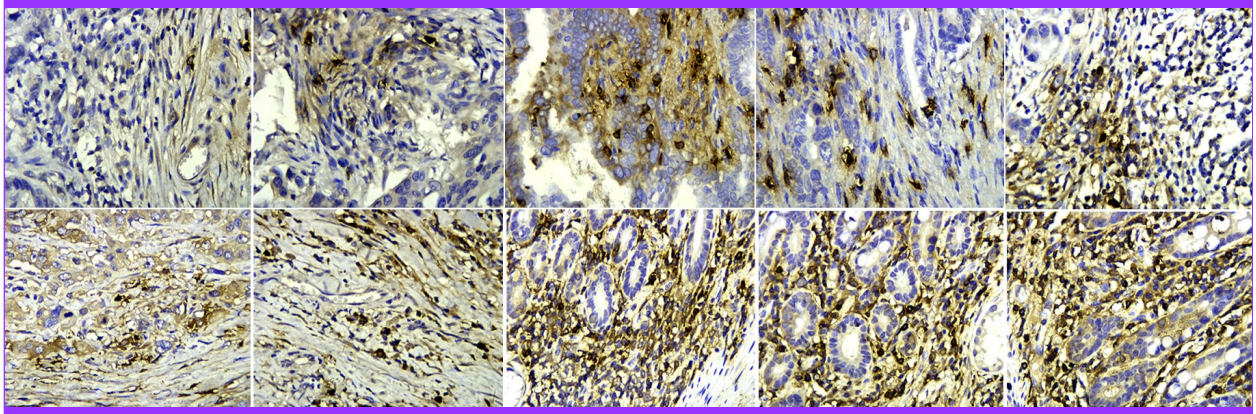

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SLC39A1 contributes to gemcitabine resistance of pancreatic ductal adenocarcinoma by activating AMPK signaling

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Abstract

Gemcitabine is a common first-line chemotherapy agent, but gemcitabine resistance is a clinical challenge for pancreatic ductal adenocarcinoma patients. Solute carrier 39A1 (SLCA39A1) as a zinc regulator presents a crucial function in the modulation of malignancy progression. Here, the impact of SLC39A1 on the gemcitabine resistance of pancreatic ductal adenocarcinoma was investigated. Immunohistochemistry demonstrated that the SLC39A1 expression was significantly up-regulated in gemcitabine-resistant pancreatic ductal adenocarcinoma samples compared with gemcitabine-sensitive ones. Gemcitabine dose-dependently inhibited the viability of the cancer cells, and SLC39A1 knockdown aggravated this effect. Both mRNA and protein expression of SLC39A1 were elevated in the gemcitabine-resistant cancer cells. SLC39A1 knockdown also reversed AMP-activated protein kinase (AMPK) phosphorylation and S6K expression of cancer cells regulated by the gemcitabine resistance. SLC39A1 promotes gemcitabine resistance of pancreatic ductal adenocarcinoma by activating AMPK signaling, revealing SLC39A1 may be a potential target in patients with gemcitabine resistance.

Introduction

Pancreatic ductal adenocarcinoma, one prevailing cancer globally, accounts for 80% of pancreatic cancer (Hu et al., 2021). It is prone to be neglected in the early stage as its symptoms are embodied in anomalies of the alimentary system, such as chronic gastritis, icterus, and relapsing pancreatitis, leading to pancreatic ductal adenocarcinoma patients typically diagnosed at an advanced degree (Nimmakayala et al., 2021).

While operational resection provides the choicest opportunity for potential remedy, it is difficult to resect all lesions completely and is accompanied by high postoperative recurrence due to the characteristic of easy metastasis and strong local invasive growth ability of pancreatic ductal adenocarcinoma (Zhou et al., 2023; Hu et al., 2024). Therefore, postoperative chemotherapy presents a crucial function in increasing the overall survival and relieving symptoms of patients (Ivey et al., 2022). However, chemotherapy resistance commonly emerged in the clinical therapy of pancreatic ductal adenocarcinoma, whose reason may be a large amount of fibrous tissue appearing in the intercepts blood supply to reduce the plasma concentration, such as the application of gemcitabine, a regular first-line chemotherapy agent (Sherman et al., 2023).

Despite continuous attempts to advance the treatment of pancreatic ductal adenocarcinoma, it still shows an unsatisfactory prognosis (Binenbaum et al., 2015; Li et al., 2023; Qi et al., 2023; Xu et al., 2023). Therefore, a comprehensive understanding of the molecular mechanisms and gene modifications in pancreatic ductal

adenocarcinoma progression and chemoresistance is urgently required for the improvement of therapeutic efficiency.

Zinc, as a messenger in the organism, is critical for metabolism and the modulation of various biological pathways, including oxidative stress, apoptosis, proliferation, and gene expression (Skrajnowska et al., 2019). The transfer approach of zinc into cells that is obliged to the specific transporters is similar to other metallic elements. The solute carrier 39A (SLCA39A) family, one Zrt, Irt-like protein, contributes to the locomotion of zinc on the surface of the nuclear envelope, playing an essential role in intracellular and extracellular zinc homeostasis regulation (Alluri et al., 2020). Moreover, it has been identified that the SLC39A family is involved in several types of cancers, including hepatocellular carcinoma, prostate cancer, lung cancer, colorectal cancer, and esophageal carcinoma (Xu et al., 2014; Cui et al., 2015; Xu et al., 2016; Sheng et al., 2017). It has been found that SLC39A factors are correlated with the diagnosis and prognosis of multiple cancer models, such as the precious prognostic value in gastric cancer of all SLC39A family numbers (Ding et al., 2019). More than that, it has been revealed that SLC39A4 is a potential diagnostic and prognostic biomarker for pancreatic ductal adenocarcinoma patients (Xu et al., 2014). The SLC39A family presents a crucial function in the modulation of malignancy progression, but the function of SLC39A1 in pancreatic ductal adenocarcinoma development, especially the modulation of gemcitabine resistance of pancreatic ductal adenocarcinoma, is still obscure. Accordingly, attention was directed towards the influence of SLC39A1 on gemcitabine resistance in pancreatic ductal adenocarcinoma.

Materials and Methods

Collection of samples

Ten pancreatic ductal adenocarcinoma samples were collected (comprising 5 gemcitabine-resistance samples and 5 gemcitabine-sensitive samples) from May 2012 to July 2018. The patients were diagnosed with stages IB to III based on histopathological analysis and subsequently underwent postoperative gemcitabine therapy. Following the collection of all samples, the expression of SLC39A1 was analyzed by immunohistochemistry.

Cell culture and transfection

The BxPC3, Panc1, CFPAC-1, MIA PaCa-2, and SW1990 cells were maintained in the lab. The BxPC3, Panc1, CFPAC-1, MIA PaCa-2, and SW1990 cells were incubated in the DMEM medium (Gibco, USA) comprising streptomycin (0.1 mg/mL Gibco, USA), penicillin (100 units/mL, Gibco, USA), and fetal bovine serum (10%, Gibco, USA), at 37 °C and 5% CO2. The control siRNA, SLC39A1 siRNA1, siRNA2, and siRNA3 were synthesized and obtained from RiboBio, China. After agents, namely siRNA, SLC39A1 siRNAs, and Lipofectamine 3000 (Life Technologies, USA), were diluted by serum-free Opti-MEM medium, siRNA and SLC39A1 siRNAs were respectively mixed with lipofectamine 3000 for 5 mins. BxPC3 was cultured in the above mixture for 3 days at 37°C to achieve transfection.

CCK-8 assays

The cell viability was tested by the CCK-8 assays (Wang et al., 2024). Around 5 × 10^3 cells were plated in 96-well plates. The cells were used for the transfection or treatment and were added with a CCK-8 solution (KeyGEN Biotech, China) and cultured for another 2 hours at 37° C. The absorbance (450 nm) was analyzed by applying an ELISA browser (Bio-Tek EL 800, USA).

Quantitative reverse transcription-PCR (qRT-PCR)

TRIZOL (Biosntech, China) was applied to extract the total RNAs, followed by the first-strand cDNA synthesis (Thermo, USA) (Ma et al., 2022). The SYBR-Green (Takara Biotechnology, Co., Lt., China) was used to carry out the qRT-PCR. The primer sequences are as

Box 1: Western Blot

Principle

The fundamental principle entails acquiring information regarding the expression of particular proteins within analyzed cells or tissues. This is achieved by immersing cells or biological tissue samples, processed through gel electrophoresis, in specific antibodies, thereby imparting coloration to the target proteins.

Requirements

Chemiluminescence detection kit (Amersham Biosciences, USA); BCA protein quantification kit (Abbkine, USA); Primary antibodies from CST, USA (SLC39A1, AMPK, p-AMPK, S6K, p-S6K and β-actin); PVDF membranes (Millipore, USA); RIPA buffer (CST, USA); Second antibodies (Abcam, USA); SDS-PAGE;

Procedure

Step 1: Total proteins were extracted using the RIPA buffer (100 mM, 400 µL per 1x10^7 cells), followed by quantification of the proteins using the BCA kit. Subsequently, the proteins were denatured by boiling in water for 5 min.

Stage 2: The proteins at the same concentration were subjected to SDS-PAGE and transferred to PVDF membranes, followed by the incubation with 5% milk and with the primary antibodies at 4°C overnight.

Step 3: The corresponding second antibodies were used for incubating the membranes for 1 hour at room temperature, followed by the visualization by using a chemiluminescence detection kit.

References

Marin et al., 2019

References (Video)

Han et al., 2023; Jiang et al., 2022; Lim et al., 2021

follows: SLC39A1 F: 5′-CGGGATCCACAGCCACCAT-GGGGCCCT-3′, R: 5′-CGGAATTCTTAGATTTGGACA-AAGAGAAGGCCAGTGAGC-3′; GAPDH F: 5′-GGGC-TGCTTTTAACTCTGGT-3′, R: 5′-GCAGGTTTTTCTAG-ACGG-3′.

Statistical analysis

Data were expressed as mean ± SD, and the statistical analysis was conducted using GraphPad Prism 7. The unpaired Student's t-test was used to compare the difference between the two groups. P<0.05 was considered as statistically significant.

Results

Expression of SLC39A1 in gemcitabine-resistance pancreatic ductal adenocarcinoma samples

To assess the potential correlation of SLC39A1 with the gemcitabine resistance of pancreatic ductal adenocarcinoma, the SLC39A1 expression was assessed in the clinical pancreatic ductal adenocarcinoma samples. Immunohistochemistry revealed that the expression of SLC39A1 was significantly elevated in the gemcitabine-resistance pancreatic ductal adenocarcinoma samples (n=5) compared with gemcitabine-sensitive pancreatic ductal adenocarcinoma samples (n=5), suggesting that SLC39A1 is closely associated with gemcitabine resistance of pancreatic ductal adenocarcinoma in the clinical context (Figure 1A).

Expression of SLC39A1 in pancreatic ductal adenocarcinoma cells

Next, the correlation of SLC39A1 with gemcitabine resistance in pancreatic ductal adenocarcinoma cells was further analyzed. To this end, the pancreatic ductal adenocarcinoma cells, including BxPC3, Panc1, MIA PaCa-2, CFPAC-1, and SW1990 cells, were treated with gemcitabine at doses of 0, 10, 50, 100, 200, 500, and 750 nM. CCK-8 assays showed that the treatment of gemcitabine dose-dependently reduced the cell viability in the BxPC3, Panc1, CFPAC-1, MIA PaCa-2, and SW1990 cells, meanwhile, the cell viability of BxPC3, Panc1, and MIA PaCa-2 cells was significantly higher than that of

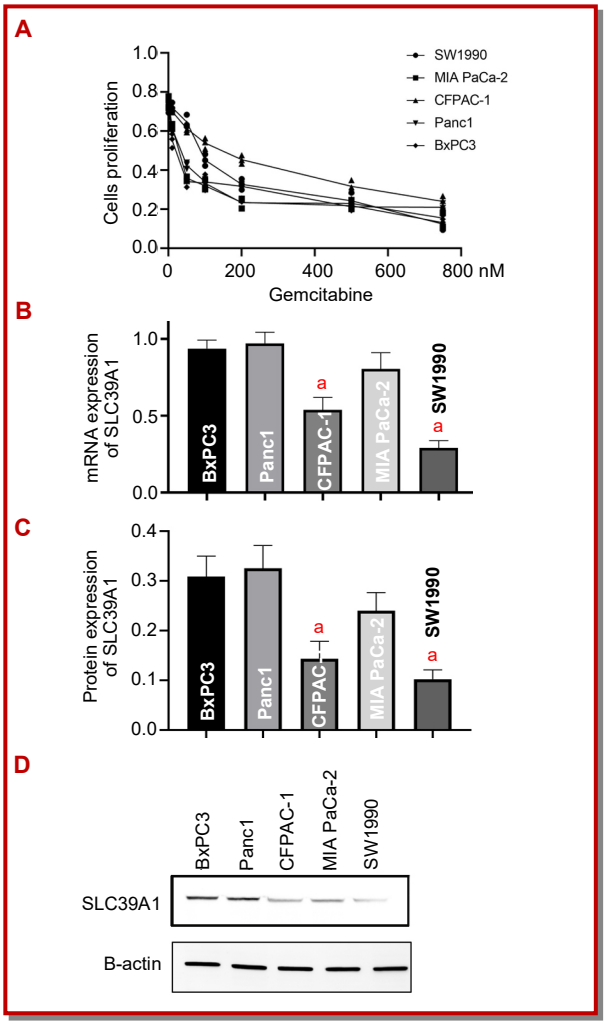

Figure 2: The expression of SLC39A1 in the pancreatic ductal adenocarcinoma cells. (A) The cell proliferation of BxPC3, Panc1, CFPAC-1, MIA PaCa-2, and SW1990 cells were treated with gemcitabine at different concentrations. The cell viability was measured by CCK-8 assays in the cells. (B and C) The mRNA and protein expression of SLC39A1 in BxPC3, Panc1, CFPAC-1, MIA PaCa-2, and SW1990 cells with the administration of gemcitabine at the doses of 750 nM. (D) The protein blots of SLC39A1 in BxPC3, Panc1, CFPAC-1, MIA PaCa-2, and SW1990 cells with the administration of gemcitabine at the doses of 750 nM. Data are mean ± SD; [a]p< 0.01

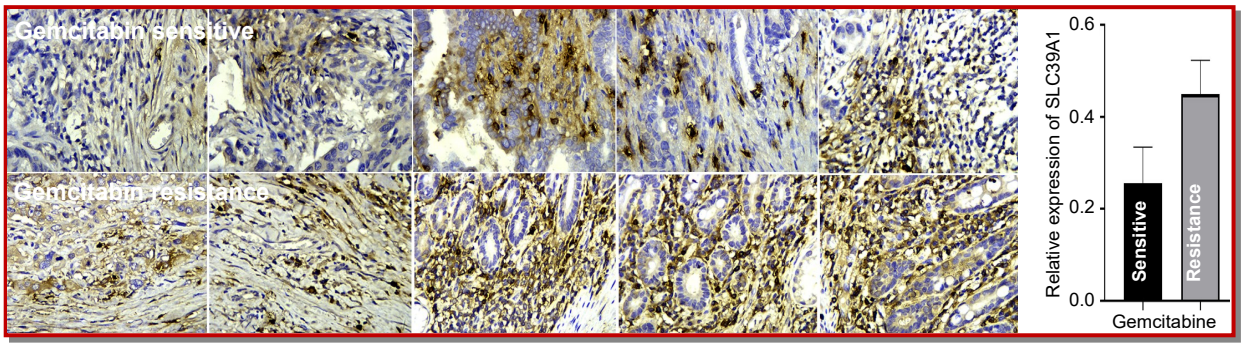

Figure 1: The expression of SLC39A1 in the gemcitabine-sensitive (upper row) and -resistance (lower row) pancreatic ductal adenocarcinoma samples. n=5 in each group. The expression of SLC39A1 was analyzed by immunohistochemistry

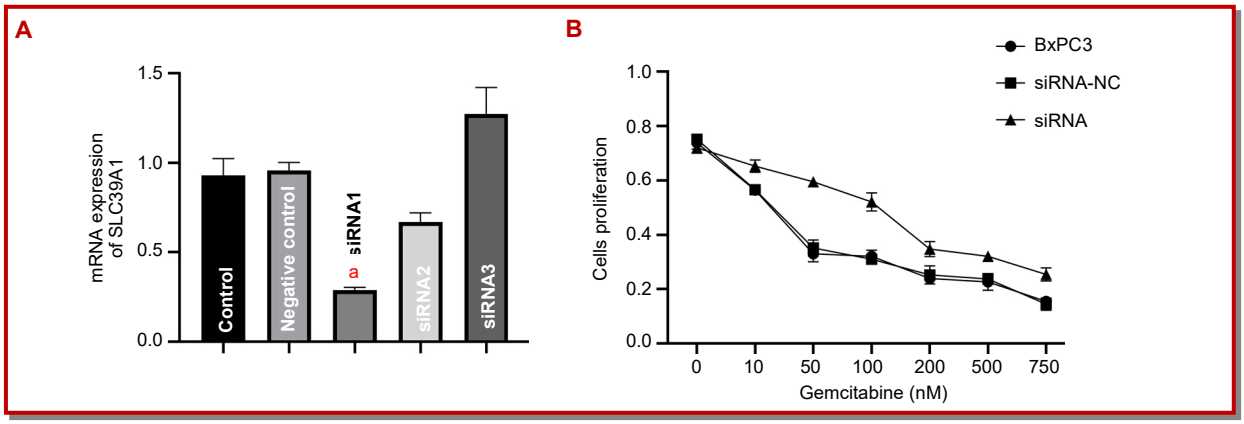

Figure 3: SLC39A1 contributed to gemcitabine-resistance in the pancreatic ductal adenocarcinoma cells. (A) The mRNA expression level of SLC39A1 in the BXPC3 cells transfected by the control siRNA, SLC39A1 siRNA1, SLC39A1 siRNA2, and SLC39A1 siRNA3. (B) The cell proliferation of BXPC3 cells with the corresponding transfection and the administration of gemcitabine at different concentrations. [a]p<0.01.

CFPAC-1 and SW1990 with gemcitabine at the concentration of 750 nM (Figure 2A). Therefore, BxPC3, Panc1, and MIA PaCa-2 cells were selected as gemcitabine-resistant pancreatic ductal adenocarci-noma cells, and 750 nM gemcitabine was regarded as the concentration of drug resistance of cells for conse-quent studies. The expression level of SLC39A1 in all cell types exposed to gemcitabine at a concentration of 750 nM was determined using qRT-PCR and western blot approaches. Significantly, the mRNA expression of SLC39A1 was up -regulated in the BxPC3, Panc1, and MIA PaCa-2 cells relative to that in the CFPAC-1 and SW1990 cells (Figure 2B). Meanwhile, western blot analysis identified similar results in the system (Figure 2C). Taken together, these data imply that SLC39A1 may potentially participate in the regulation of gemcitabine resistance of pancreatic ductal adenocarcinoma.

Modulation of gemcitabine resistance

Then, the role of SLC39A1 in the modulation of gemcitabine resistance in pancreatic ductal adenocarcinoma was further investigated. To this end, the BXPC3 cells were treated with control siRNA, SLC39A1 siRNA1, SLC39A1 siRNA2, and SLC39A1 siRNA3, among which the SLC39A1 siRNA1 presented the highest depletion efficiency in the cells and was applied in the subsequent analysis (Figure 3A). After transfecting with control siRNA and SLC39A1 siRNA1, and treating with a series of concentrations (0, 10, 50, 100, 200, 500, and 750 nM) of gemcitabine, the cell viability of BXPC3 cells was further assessed using the CCK-8 experiment. The treatment of gemcitabine significantly reduced cell viability

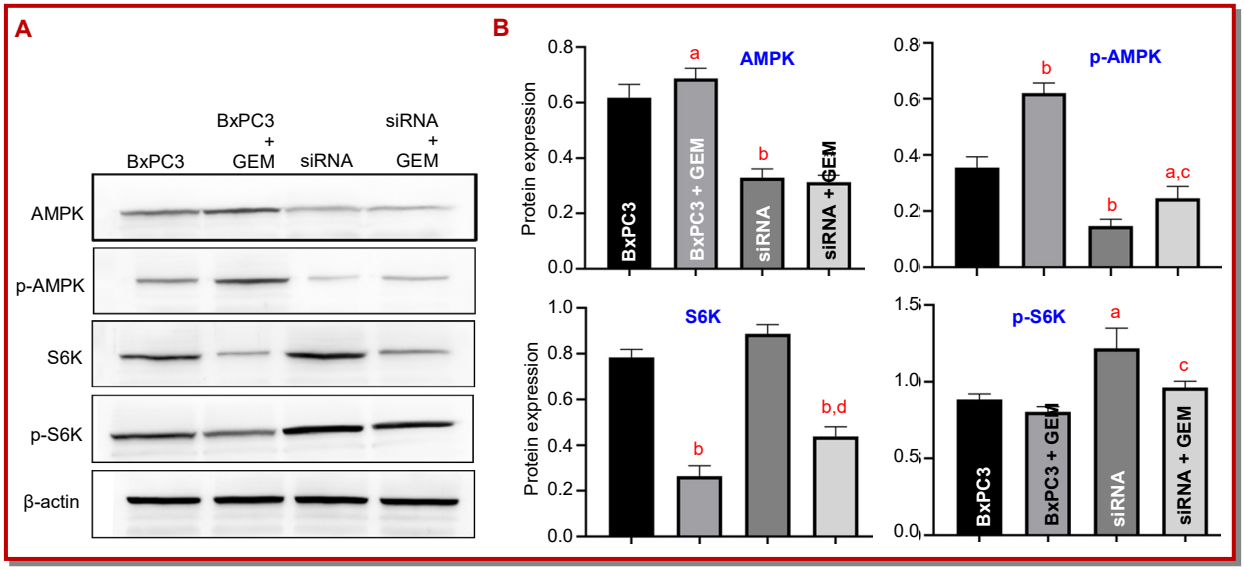

Figure 4: SLC39A1 promoted gemcitabine resistance by activating AMPK signaling in the pancreatic ductal adenocarcinoma cells. (A) The protein blots of AMPK, p-AMPK, S6K, p-S6K, and β-actin in BxPC3 cells with the corresponding treatments. (B) The protein expression of AMPK, p-AMPK, S6K, and p-S6K in BxPC3 cells with the corresponding treatments. Statistic significant differences were indicated: [a]/[b]p<0.05/0.01 *vs*. BxPC3; [c]/[d]p<0.05/0.01 *vs*. SiRNA

of BXPC3 cells, in which the depletion of SLC39A1 enhanced the inhibitory effect of gemcitabine in cell viability, indicating that SLC39A1 promotes gemcitabine resistance in the pancreatic ductal adenocarcinoma cells (Figure 3B).

Activating AMPK signaling

Next, the mechanism of SLC39A1-mediated gemcitabine resistance in pancreatic ductal adenocarcinoma was further explored. The protein expression level of AMPK, S6K, phosphorylated AMPK, and phosphorylated S6K of BXPC3 cells transfected by SLC39A1 siRNA1 as well as administrated with 750 nM gemcitabine was determined by adopting the western blot method. Significantly, it was observed that the phosphorylation of AMPK was enhanced while the expression of S6K was reduced by the treatment of gemcitabine, in which the SLC39A1 knockdown could reverse this effect in the BXPC3 cells (Figure 4A-B). Together these suggest that SLC39A1 promotes gemcitabine resistance by activating AMPK signaling in the pancreatic ductal adenocarcinoma cells.

Discussion

Abnormal gene expression is closely associated with gemcitabine resistance in treating multiple carcinomas. For example, the up-regulation of TRIM31 promotes gemcitabine resistance by the activation of NF-κB signaling in pancreatic cancer (Yu et al., 2018). The elevation of ADAM28 predicts a poor prognosis and confers gemcitabine resistance in pancreatic ductal adenocarcinoma patients (Wei et al., 2019). GLI/SOX2 axis regulates the gemcitabine resistance of pancreatic ductal adenocarcinoma (Jia et al., 2019). Enhanced cytosolic 5′-nucleotidase 1A also affects the gemcitabine resistance of pancreatic ductal adenocarcinoma (Patzak et al., 2019). Moreover, it has been identified that SLC39A1 is involved in cancer progression (Costello et al., 2016; Wang et al., 2020; Zhang et al., 2021; Yu et al., 2022), but the role of SLC39A1 in pancreatic ductal adenocarcinoma development has not been reported. In this study, the expression of SLC39A1 in gemcitabine-resistant pancreatic ductal adenocarcinoma samples and cells was found to be significantly up-regulated compared to gemcitabine-sensitive ones, using IHC, qRT-PCR, and western blot approaches. These data implied that SLC39A1 may be involved in the modulation of gemcitabine resistance of pancreatic ductal adenocarcinoma. Therefore, SLC39A1 was considered the core target for subsequent experiments. The difference in cell viability of BxPC3 between normal and SLC39A1 knockdown conditions was further compared under various concentrations of gemcitabine. The data demonstrated that SLC39A1's contribution to gemcitabine resistance in pancreatic ductal adenocarcinoma cells. This research revealed a novel function of SLC39A1 in gemcitabine resistance in pancreatic ductal adenocarcinoma, offering valuable evidence for its role in the chemoresistance of cancer patients. Nevertheless, it is still urgent to investigate the exact mechanisms that SLC39A1 contributed to the gemcitabine resistance of pancreatic ductal adenocarcinoma.

AMPK, a key molecule in the regulation of bioenergy metabolism, and S6K, a multifunctional serine/threonine protein kinase, constitute the AMPK signaling pathway that is essential for maintaining organismic glucose balance. Moreover, the AMPK signaling pathway, as a crucial cellular pathway, widely participates in the regulation of gemcitabine resistance of pancreatic ductal adenocarcinoma. It has been reported that the inhibition of YAP caused by AMPK-induced HMGCR down-regulation can sensitize pancreatic ductal adenocarcinoma cells to gemcitabine (Zhou et al., 2019). Gemcitabine promotes autophagy and apoptosis through the AMPK signaling in pancreatic ductal adenocarcinoma (Zhu et al., 2018). Ultraviolet increases gemcitabine sensitivity by activating AMPK in pancreatic ductal adenocarcinoma (Adachi et al., 2011). Our mechanism investigation further revealed that the phosphorylated level of AMPK ascended but the expression level of S6K declined in pancreatic ductal adenocarcinoma cells with gemcitabine resistance. Meanwhile, the above alterations were dramatically reversed with the knockdown of SLC39A1.

These data identified an unreported correlation of SLC39A1 with the AMPK signaling pathway in the modulation of gemcitabine resistance of pancreatic ductal adenocarcinoma, namely SLC39A1 promoted gemcitabine resistance by activating the AMPK signaling pathway in pancreatic ductal adenocarcinoma cells.

Conclusion

SLC39A1 contributes to gemcitabine resistance by activating the AMPK signaling pathway, highlighting its potential as a therapeutic target for combating drug resistance in pancreatic ductal adenocarcinoma patients.

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Ethical Issue

The samples applied in this investigation received written approval from the pancreatic ductal adenocarcinoma patients. This study conformed to the experimental guidelines of the World Medical Association and the Ethics Committee of Jiaxing First Hospital [LS2018-175].

Conflict of Interest

Authors declare no conflict of interest

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