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ORIGINAL RESEARCH

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KIF2C promotes doxorubicin resistance in ovarian cancer cells and increases cancer cell glycolysis by upregulating PKM2

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Abstract

Ovarian cancer stands as one of the most frequently diagnosed malignant tumors among women. Doxorubicin (DOX), a potent anthracycline chemotherapeutic agent, is widely used in the treatment of ovarian cancer. However, resistance to DOX remains a significant challenge. Kinesin family member 2C (KIF2C), a member of the Kinesin-13 family, has been associated with various cancers, but its specific involvement in the resistance of ovarian cancer to DOX remains to be elucidated. This study investigates the role of KIF2C in ovarian cancer DOX resistance. Through meticulous experimentation, we successfully constructed two DOX-resistant ovarian cancer cell lines and found that KIF2C was overexpressed in these cells, promoting cell growth. By silencing KIF2C, we were able to re-sensitize the DOX-resistant cells to the drug and significantly impair their migratory capabilities. Our mechanistic studies revealed that KIF2C upregulates the expression of pyruvate kinase isozyme type M2 (PKM2), thereby enhancing glycolysis—a key metabolic pathway—in DOX-resistant ovarian cancer cells. In summary, KIF2C contributes to DOX resistance and enhances glycolysis in ovarian cancer cells by upregulating PKM2, suggesting that KIF2C may serve as a promising therapeutic target for circumventing drug resistance in ovarian cancer treatments.

Keywords

Ovarian cancer; Doxorubicin (DOX); KIF2C; Glycolysis; PKM2

1. Introduction

Ovarian cancer is a prevalent and lethal malignancy among women, ranking as a principal cause of mortality from gynecological cancers [1]. With advancements in surgical techniques and chemotherapy, early-stage ovarian cancer patients often have favorable prognoses [2]. Doxorubicin (DOX) is an anthracycline chemotherapy drug that is effective in the treatment of a variety of malignancies, including ovarian cancer [3]. However, in advanced metastatic cancer, especially when it recurs after chemotherapy, the utility of chemotherapy is compromised by severe systemic toxicity and the emergence of drug resistance. The defiance of ovarian cancer cells to DOX poses a formidable barrier in treatment. Resistance can be caused by various mechanisms, including drug efflux, enhanced DNA repair capabilities, increased anti-apoptotic signals, and changes in drug metabolism pathways [4, 5]. In response, researchers are investigating strategies like the development of novel drugs, combination chemotherapy, and innovative drug delivery methods to surmount DOX resistance in ovarian cancer. There is an urgent need to delineate the mechanisms underlying drug resistance in this cancer to underpin the development of targeted therapies.

The Kinesin-13 family, including KIF2A, KIF2B, KIF2C and KIF24, is involved in mitotic regulation [6]. Among them, KIF2C stands out for its multifaceted functions in spindle assembly, sister chromatid segregation, and error correction through the modulation of microtubule dynamics [7]. KIF2C is overexpressed in certain tumors and promotes their progression [7]. In cervical cancer, KIF2C promotes the cell growth of by inhibiting the p53 pathway [8], while in hepatocellular carcinoma (HCC), it drives progression through the promotion of epithelial-mesenchymal transition (EMT) [9]. KIF2C regulates DOX resistance by promoting stable increase of glycolysis of PKM2 protein in breast cancer [10]. Analysis of The Cancer Genome Atlas (TCGA) and Clinical Proteomic Tumor Analysis Consortium (CPTAC) data has revealed upregulated KIF2C expression in ovarian cancer tissues, identifying it as a potential molecular marker for ovarian cancer in several studies [11], but the mechanism of action of KIF2C in ovarian cancer remains unclear.

This study aims to reveal the role of KIF2C in ovarian cancer DOX resistance. Our findings indicate that an elevated expression of KIF2C in ovarian cancer cells fosters their proliferation and is even more pronounced in cells that have developed resistance to DOX. KIF2C knockdown induces the

sensitivity of drug-resistant cells to DOX, and inhibits the migration and invasion of DOX-resistant cells. Consequently, we propose that KIF2C may be a promising therapeutic target for countering DOX resistance in ovarian cancer treatment.

2. Materials and methods

2.1 Cell culture and treatment

All cell lines including IOSE80, SKOV3 as well as A2780, were provided by American Type Culture Collection (ATCC, VA, USA). These cell lines were cultured in Dulbecco's Modified Eagle Medium (DMEM, 12800017, Gibco, Grand Island, NY, USA) supplemented with 10% fetal bovine serum (FBS). The medium was supplemented with 10% FBS. DOX was purchased from Sigma (232120, Sigma, Burlington, MA, USA) and treated into SKOV3 and A2780 cells at the concentration of 1 μM for 24 h. The siRNAs of negative control (NC) or KIF2C (bought from Riobio, Guangzhou, Guangdong, China) and pcDNA3.1-PKM2 or vector plasmids were all transfected into ovarian cancer cells using Lipofectamine® 2000 (1168019, Invitrogen, Thermo Fisher, Carlsbad, CA, USA). The transfection was allowed to proceed for 24 h before conducting subsequent experimental procedures.

2.2 The construction of DOX-resistant cells and the detection of cell viability

The SKOV3 as well as A2780 cells were repeatedly exposed to increased concentrations of DOX over a 12-month period. Initially, the cells were treated with a low concentration of 0.01 μM DOX, with the dosage incremented every four generations. The resultant DOX-resistant cells were cultured in DMEM supplemented with a steady concentration of 1 μM DOX, leading to the establishment of the SKOV3/DOX and A2780/DOX cell lines. SKOV3/DOX as well as A2780/DOX cells were cultured wit DOX (Sigma, USA). Cell viability was conducted with 3-(4,5)-dimethylthiahiazo (-z-y1)-3,5-diphenytetrazoliumromide (MTT) kit (ST316, Beyotime, Beijing, China). In brief, cells were seeded into 96-well plates and after incubation with the MTT solution for 4 h, they were solubilized in Dimethyl Sulfoxide (DMSO, D2650, Sigma, Burlington, MA, USA). A volume of 150 μL of DMSO was added to each well. The absorbance was then measured at 490 nm using a microplate reader.

2.3 Colony formation assay

SKOV3/DOX as well as A2780/DOX cells were cultured for two weeks. Then, Paraformaldehyde (PFA) (4%)-fixed colonies were stained with crystal violet solution (0.5%) for 2 h and counted. Colonies consisting of more than 50 cells were considered for counting. The experiment was performed in triplicate to ensure reproducibility.

2.4 Transwell assay

Cells were plated into the upper of transwell chambers with 20% matrigel in culture medium. After 24 h, cells in upper were removed, and the remaining cells were fixed, as well as stained.

2.5 Wound-healing assay

A 10-μL pipette tip was used to create a scratch, after which the SKOV3/DOX as well as A2780/DOX cells were washed twice. Images of the wound were captured at 0 and 24 h to determine the extent of wound closure. The extent of wound closure was determined by measuring the wound width at five different points using ImageJ software (8.0, National Institutes of Health, Bethesda, MD, USA).

2.6 Glucose consumption, lactic acid production and Adenosine triphosphate (ATP) production test

The glycolysis levels of SKOV3/DOX and A2780/DOX cells were assessed using specific kits to measure glucose consumption, lactic acid production, and ATP production. For the measurement of glucose consumption, cells were seeded into 6-well plates and incubated for 24 h in a glucose-deprived medium. The medium was then collected and the glucose concentration was measured using the Glucose Assay Kit (ab136955, Abcam, Cambridge, UK). To gauge lactic acid production, the culture supernatant was collected after 24 h of incubation, and the lactic acid content was quantified with the Lactate Assay Kit (ab65330, Abcam, Cambridge, UK). ATP levels were measured using the ATP Assay Kit (ab83355, Abcam, Cambridge, UK) following the manufacturer's instructions. Briefly, cells were lysed and the lysate was added to the reaction mix. The luminescence output was then recorded using a microplate reader, and ATP concentrations were determined by referencing an ATP standard curve. Each assay was conducted in triplicate to ensure the precision and reliability of the results.

2.7 Immunoblot assays

To extract protein from the cells, Radio Immunoprecipitation Assay (RIPA) lysate was used to ensure complete lysis. The extracted protein was quantified with a bovine serum albumin (BCA) reagent, separated via Sodium Dodecyl Sulfate-Polyacrylamide Gel Electrophoresis (SDS-PAGE), and subsequently transferred onto a polyvinylidene fluoride (PVDF) membrane. The membranes were blocked with 5% milk for 1 h, and then the primary antibodies were added as well as incubated at 4 ℃ overnight. Primary antibodies KIF2C (Abcam, Cambridge, UK, ab187652; 1:1000), PKM2 (Abcam, Cambridge, UK, ab8555; 1:1000) and β-actin (Abcam, Cambridge, UK, ab8226; 1:3000). Afterward, the membrane was probed with secondary antibodies for 1 h. The protein bands were visualized using chemiluminescence and then documented photographically.

2.8 Statistics

GraphPad 5.0 software (Graphpad company, Boston, MA, USA) was used and performed. Data were represented as mean $\pm$ Standard Deviation (SD). $p < 0.05$ was thought as significant.

3. Results

3.1 KIF2C was overexpressed in ovarian cancer and promoted cell growth

To explore the potential role of KIF2C in ovarian cancer, we initially assessed its expression levels in both ovarian cancer tissues and cell lines. TCGA database indicated the high transcripts per million value of KIF2C in ovarian cancer tissues (Fig. 1a). Further through Immunoblot, our data revealed that KIF2C was high expression in two types of ovarian cancer cell lines, SKOV3 and A2780, compared to human normal ovarian epithelial cell line IOSE80 (Fig. 1b). Subsequently, we introduced two siRNAs targeting KIF2C into SKOV3 and A2780 cells to reduce its expression, and the efficacy of this silencing was confirmed via Immunoblot (Fig. 1c). Through MTT assays, we noticed the depletion of KIF2C suppressed the viability of SKOV3 and A2780 cells, with the decreased OD490 value (Fig. 1d). Similarly, colony formation assays confirmed that KIF2C depletion restrained the growth of SKOV3 as well as A2780 cells (Fig. 1e). Consequently, our findings suggest that KIF2C is overexpressed in ovarian cancer and contributes to cellular proliferation.

3.2 Knockdown of KIF2C induced sensitivity of DOX-resistant ovarian cancer cells to DOX

Subsequently, we detected the effects of KIF2C on the sensitivity of DOX-resistant ovarian cancer cells to DOX. Two DOX-resistance ovarian cancer cell lines, SKOV3 DOX resistance (SKOV3 DOX) and A2780 DOX resistance (A2780 DOX), were successfully constructed. We observed a significant upregulation of KIF2C in SKOV3 DOX and A2780 DOX cells compared to their non-resistant counterparts, SKOV3 or A2780 cells (Fig. 2a). Then we detected the IC_{50} value of these 4 cell lines. We noticed thee DOX-resistance of SKOV3 or A2780 cells dramatically increased the IC_{50} value, compared to SKOV3 or A2780 cells (from 15.78 to 146.9 μg/mL, from 11.9 to 119.2 μg/mL, respectively, Fig. 2b). Further, KIF2C was depleted in SKOV3 DOX and A2780 DOX cells, and the silencing efficiency was also confirmed by Immunoblot (Fig. 2c). Interestingly, we found that the knockdown of KIF2C significantly reduced the IC_{50} value of SKOV3 DOX and A2780 DOX cells, indicating an increased sensitivity to DOX (from 116.5.9 to 46.95, from 149 to 66.55 μg/mL, respectively, Fig. 2d). Similarly, through colony formation assays, we noticed DOX treatment decreased colony numbers of SKOV3 DOX or A2780 DOX cells, whereas KIF2C depletion further decreased colony numbers, suggesting the suppression of cell growth (Fig. 2e). Collectively, the elimination of KIF2C induced sensitivity to DOX in DOX-resistant ovarian cancer cells.

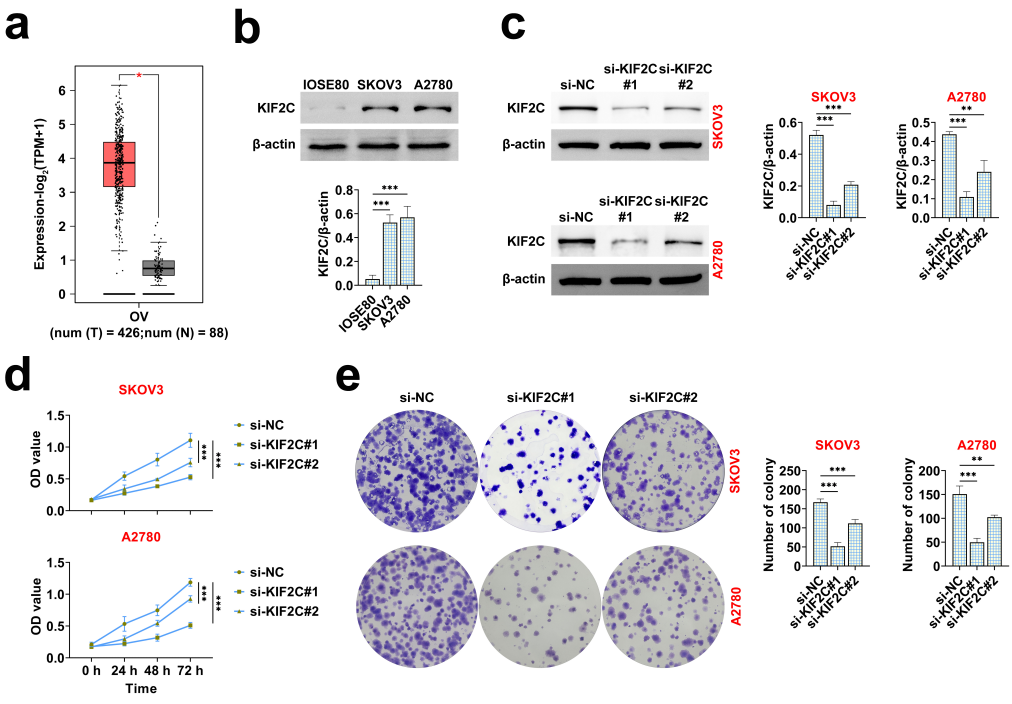

FIGURE 1. KIF2C was overexpressed in ovarian cancer and KIF2C promoted cell growth. (a) TCGA database showed the transcripts per million (TPM) value of KIF2C in 426 ovarian cancer tissues and 88 normal tissues. (b) Immunoblot assays showed the expression of KIF2C in IOSE80, SKOV3, and A2780 cell lines. (c) Immunoblot assays showed the expression of KIF2C in SKOV3 and A2780 cells upon the transfection of NC or KIF2C siRNAs. (d) MTT assays showed the growth of SKOV3 and A2780 cells upon the transfection of NC or KIF2C siRNAs for 24, 48 and 72 h. The OD490 value was measured. (e) Colony formation assays showed the growth of SKOV3 and A2780 cells upon the transfection of NC or KIF2C siRNAs. The numbers of colony were counted. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. NC, negative control; OV, ovarian cancer; OD, Optical Density; KIF2C, Kinesin family member 2C.

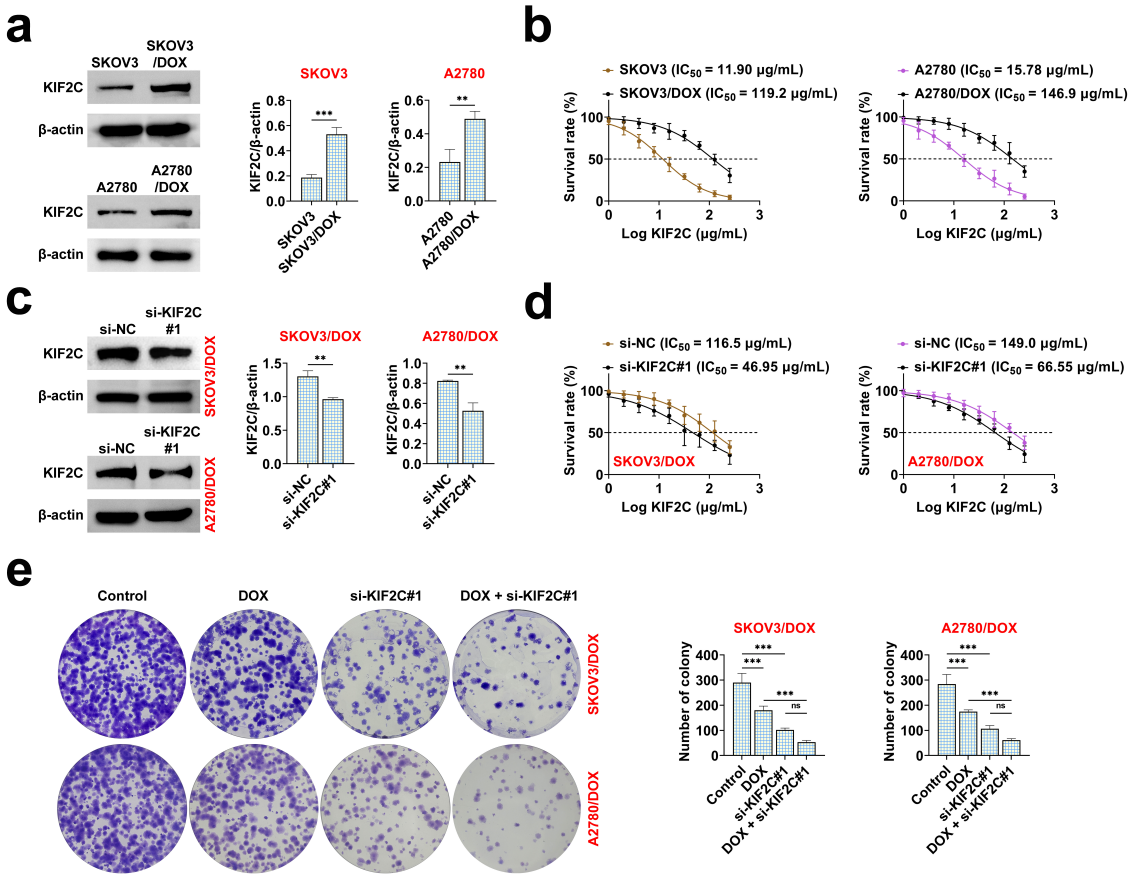

FIGURE 2. Knockdown of KIF2C induced sensitivity of DOX-resistant cells to DOX. (a) Immunoblot assays showed the expression of KIF2C in SKOV3, SKOV3 DOX resistance (up), A2780, and A2780 DOX resistance (down) cells. (b) MTT assays showed the IC_{50} value of SKOV3, SKOV3 DOX resistance (left), A2780, and A2780 DOX resistance (right) cells. (c) Immunoblot assays showed the expression of KIF2C in SKOV3 DOX resistance and A2780 DOX resistance cells upon the transfection of NC or KIF2C siRNAs. (d) MTT assays showed the IC_{50} value of SKOV3 DOX resistance and A2780 DOX resistance cells upon the transfection of NC or KIF2C siRNAs. (e) MTT assays showed the growth of SKOV3 DOX resistance and A2780 DOX resistance cells upon the transfection of NC or KIF2C siRNAs. The numbers of colony were counted. $^{**}p < 0.01$, $^{***}p < 0.001$. NC, negative control; DOX, Doxorubicin; IC, Half maximal inhibitory concentration; KIF2C, Kinesin family member 2C.

3.3 Knockdown of KIF2C restrained motility of DOX-resistant ovarian cancer cells

We further investigated the effects of KIF2C depletion on the motility of SKOV3 DOX and A2780 DOX cells. Through wound healing assays, we noticed the depletion of KIF2C increased wound width of SKOV3 DOX and A2780 DOX cells, suggesting the inhibition of cell migration (Fig. 3a). Similarly, transwell assays demonstrated that KIF2C depletion diminished the invasive potential of these cells, as evidenced by a reduction in the number of invasive cells (Fig. 3b). Therefore, our findings suggest that the elimination of KIF2C inhibits the motility of DOX-resistant ovarian cancer cells.

3.4 KIF2C up-regulated PKM2 expression and cotributes to glycolysis of DOX-resistant ovarian cancer cells

Finally, to elucidate the underlying mechanism, we scrutinized the impact of KIF2C depletion on the metabolic profile of SKOV3 DOX and A2780 DOX cells. Our findings revealed that KIF2C reduction curtailed glucose consumption, ATP production, and lactic acid production in these cells, as confirmed by the respective assay kits. This observation suggests a suppression of glycolysis (Fig. 4a). Further through Immunoblot assays, we found the depletion of KIF2C suppressed the expression of PKM2 in SKOV3 DOX and A2780 DOX cells (Fig. 4b). Interestingly, we noticed PKM2 overexpression could rescue the suppression of cell viability caused by KIF2C depletion in SKOV3 DOX and A2780 DOX cells (Fig. 4c). This correlation led us to hypothesize that KIF2C may upregulate PKM2 expression, thereby contributing to the glycolytic activity of DOX-resistant ovarian cancer cells.

4. Discussion

The development of chemotherapy resistance in ovarian cancer is a multifaceted challenge that involves a variety of intricate mechanisms [12, 13]. To overcome these challenges, new treatment strategies are being explored. Targeted therapy for ovarian cancer seeks to enhance treatment efficacy and miti-

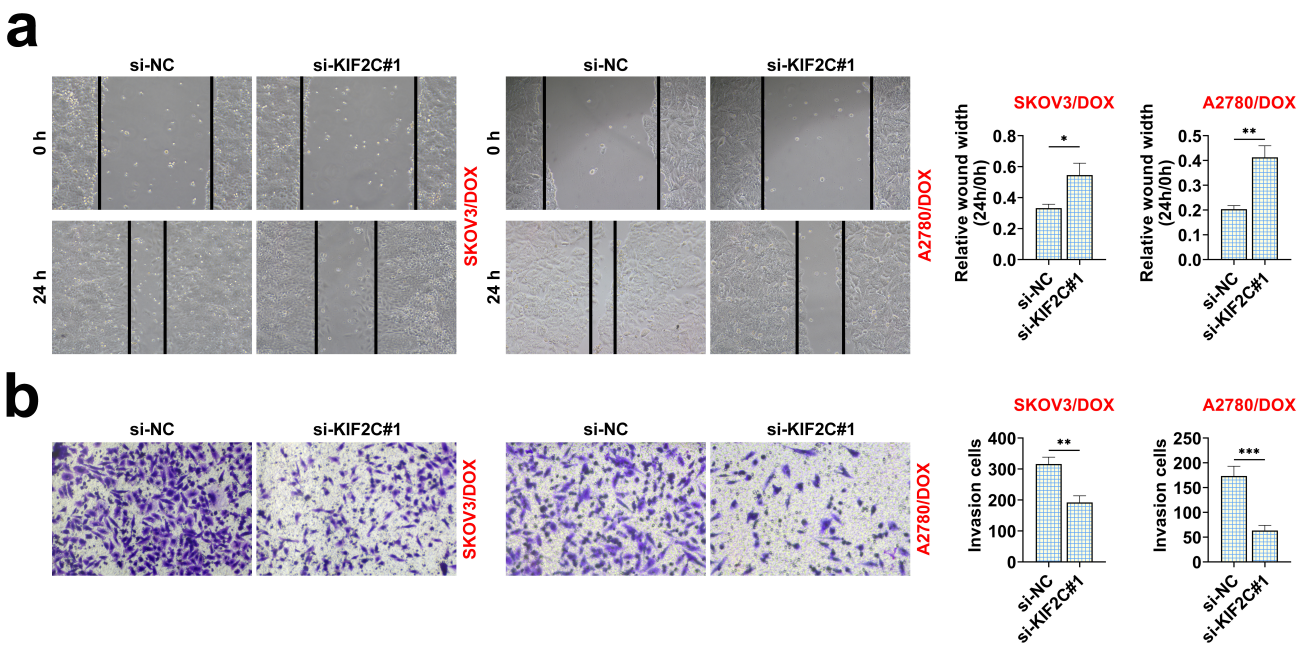

FIGURE 3. Knockdown of KIF2C restrained motility of DOX-resistant ovarian cancer cells. (a) Wound healing assays showed the migration of SKOV3 DOX resistance and A2780 DOX resistance cells upon the transfection of NC or KIF2C siRNAs. The relative wound width was measured. (b) Transwell assays showed the invasion of SKOV3 DOX resistance and A2780 DOX resistance cells upon the transfection of NC or KIF2C siRNAs. The invasive cell numbers were counted. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$. NC, negative control; DOX, Doxorubicin; IC, Half maximal inhibitory concentration; KIF2C, Kinesin family member 2C.

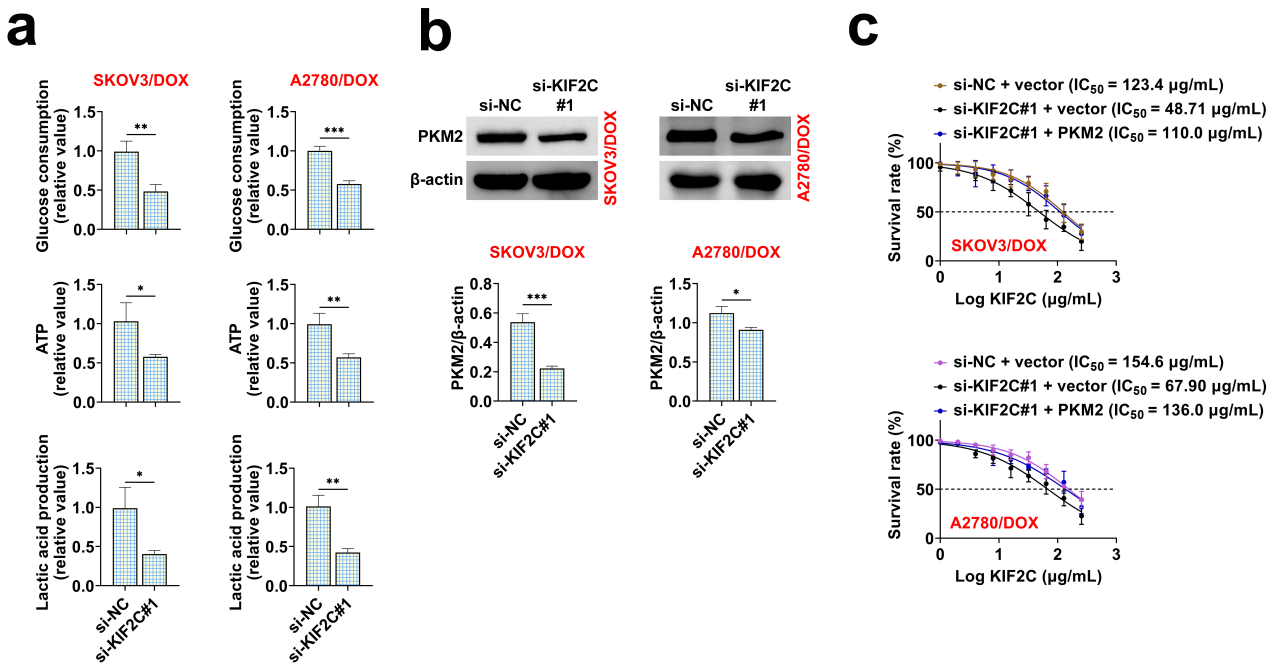

FIGURE 4. KIF2C up-regulated PKM2 expression and contributes to glycolysis of DOX-resistant ovarian cancer cells. (a) The corresponding kits showed the glucose consumption, ATP production, and lactic acid of SKOV3 DOX resistance and A2780 DOX resistance cells upon the transfection of NC or KIF2C siRNAs. (b) Immunoblot assays showed the expression of PKM2 in SKOV3 DOX resistance and A2780 DOX resistance cells upon the transfection of NC or KIF2C siRNAs. (c) MTT assays showed the IC_{50} value of SKOV3 DOX resistance (left), and A2780 DOX resistance (right) cells upon the indicated transfection. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$. NC, negative control; DOX, Doxorubicin; ATP, adenosine triphosphate; PKM2, Pyruvate kinase isozyme type M2; IC, Half maximal inhibitory concentration; KIF2C, kinesin family member 2C.

gate drug resistance by focusing on specific molecules within cancer cells [1]. The selection of targeted therapy is typically guided by the patient's genetic mutations and the characteristics of their disease, and it is often administered in conjunction with chemotherapy or other therapies to amplify its impact [3]. Interestingly, we here revealed that KIF2C overexpression in ovarian cancer stimulates the growth of cancer cells, and is further up-regulated in drug-resistant cells. Reducing KIF2C levels resensitizes drug-resistant cells to DOX and curtails their migratory and invasive capabilities. Consequently, we propose that KIF2C may be a viable therapeutic target for combating drug resistance in ovarian cancer.

The construction of DOX-resistant ovarian cancer cell lines involves identifying an appropriate cell line, incrementally increasing the concentration of DOX to elicit resistance, culturing the resistant cells in a DOX-containing medium, and validating resistance through assays such as MTT or flow cytometry. This process helps in studying the mechanisms of drug resistance, such as increased drug efflux or altered apoptosis, which is crucial for developing new strategies to overcome resistance and improve cancer treatment efficacy [14]. Significantly, we have successfully generated DOX-resistant cell lines and further ascertained the role of KIF2C in this resistance. However, the exact underlying mechanisms warrant further exploration.

KIF2C is a key microtubule depolymerase involved in chromosome separation and spindle adjustment during cell division. In the realm of oncology, KIF2C's overexpression in a variety of cancers has been linked to tumor aggression and resistance to chemotherapy. It exerts influence over tumor cell proliferation and motility by modulating microtubule dynamics and maintaining cytoskeletal stability [15]. Therefore, KIF2C is considered a potential target for cancer therapy, but its specific role in tumor development requires further study. Interestingly, through a series of *in vitro* assays, we confirmed that KIF2C was overexpressed in ovarian cancer and promotes cell growth. Moreover, the suppression of KIF2C resensitized drug-resistant cells to DOX, suggesting that KIF2C may be a critical factor in the drug resistance and progression of ovarian cancer.

PKM2 stands as a cornerstone in cancer cell metabolism and is implicated in the development of chemotherapy resistance [16]. It governs metabolic activity by catalyzing the conversion of phosphoenolpyruvate to pyruvate in the glycolytic pathway, thereby generating ATP [17]. In cancer cells, PKM2's reduced activity leads to the accumulation of glycolytic intermediates, supporting rapid proliferation. PKM2's involvement in metabolic reprogramming, cell signaling, nuclear functions, and its interaction with proteins conferring drug resistance mark it as a strategic target for overcoming chemotherapy resistance [18]. Inhibiting or modulating PKM2 activity could enhance the effectiveness of chemotherapy, and research is ongoing to develop inhibitors or modulators of PKM2 as new cancer treatment strategies. Interestingly, our data confirmed that KIF2C promotes DOX resistance in ovarian cancer cells and increases cancer cell glycolysis via targeting PKM2.

PKM2 is central to the metabolic reprogramming of cancer cells, driving glycolysis and thereby supporting the swift growth and survival of these cells. The connection between KIF2C and PKM2 is particularly relevant in the context of cancer metabolism and drug resistance. KIF2C has been shown to regulate DOX resistance in breast cancer by enhancing the stability and glycolytic activity of PKM2, highlighting a potential mechanism by which KIF2C can bolster metabolic adaptability and the survival of cancer cells. Our study corroborates these findings by showing that KIF2C upregulates PKM2 expression in DOX-resistant ovarian cancer cells, thereby increasing glycolysis and contributing to drug resistance. This association underscores the therapeutic potential of simultaneously targeting KIF2C and PKM2 to combat chemoresistance in ovarian cancer.

5. Conclusions

In summary, KIF2C contributed to DOX resistance and increased glycolysis in ovarian cancer cells by upregulating PKM2. We therefore thought KIF2C could serve as a target of ovarian cancer.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

LMT and YFG—designed the study and carried them out; prepared the manuscript for publication and reviewed the draft of the manuscript. LMT, MX, JJQ, QYW and HLZ—supervised the data collection. LMT, MX, JJQ and QYW—analyzed the data. LMT, MX and JJQ—interpreted the data. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This article does not contain any studies with human participants or animals performed by any of the authors.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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