

# MiR-19a-3p Promotes Aerobic Glycolysis in Ovarian Cancer Cells via IGFBP3/PI3K/AKT Pathway

(miR-19a-3p / ovarian cancer / aerobic glycolysis / IGFBP3 / PI3K/AKT pathway)

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**Abstract.** Aerobic glycolysis is a prominent feature of cancer. Here, we reported that miR-19a-3p promotes aerobic glycolysis in ovarian cancer cells SKVO3 and ES-2 by increased production of ATP, lactic acid, extracellular acidification (ECAR), and increased expression of PKM2, LDHA, GLUT1 and GLUT3. Further study showed that over-expression of IGFBP3, the target of miR-19a-3p, decreases aerobic glycolysis in ovarian cancer cells, while knockdown of IGFBP3 expression increases aerobic glycolysis. The rescue assay suggested that miR-19a-3p promotes aerobic glycolysis in ovarian cancer cells through targeting IGFBP3. Moreover, over-expression of miR-19a-3p or silencing of IGFBP3 expression promoted activation of AKT, which is important for aerobic glycolysis in cancer cells, indicating that miR-19a-3p promotes aerobic glycolysis in ovarian cancer cells through the IGFBP3/PI3K/AKT pathway. This suggests that miR-19a-3p and IGFBP3 may serve as potential treatment targets of ovarian cancer.

## Introduction

The statistics of global cancer 2020 reported over 300,000 new cases of ovarian cancer (OC) and approxi-

mately 210,000 cases of ovarian cancer-related deaths in the world, indicating the serious threat of ovarian cancer to women's health (Sung et al., 2021). Due to the lack of early symptoms and early diagnostic biomarkers of ovarian cancer, 70 % of ovarian cancers have progressed to advanced stage with pelvic and abdominal metastases at first diagnosis, leading to poor treatment outcomes (Lin et al., 2020). The majority of ovarian cancer patients survive less than five years (Maringe et al., 2012); therefore, it is necessary to explore the underlying mechanism of ovarian cancer in order to ensure earlier diagnosis and better treatment outcomes.

Aerobic glycolysis is the most prominent feature of tumour cells even when they are well oxygenated (Hananan et al., 2011). In tumour cells, glucose is metabolized to pyruvate, followed by conversion to lactate by lactate dehydrogenase (LDH) to circumvent the mitochondrial tricarboxylic acid cycle (Vazquez et al., 2016; Park et al., 2020). PKM2 is the M2 isoform of pyruvate kinase and serves as a sensor and regulator of tumour glucose metabolism. PKM2 often switches between tetramer and dimer forms to determine whether the conversion of glucose to pyruvate is used for energy or for biosynthetic processes (Wu et al., 2013; Li et al., 2019b). In 1924, Warburg firstly observed aerobic glycolysis; therefore, it is also known as the Warburg effect.

MicroRNAs (miRNAs) are small endogenous non-coding RNAs consisting of approximately 20 to 25 nucleotides, and they target one or more mRNAs and regulate gene expression through inhibiting the translation of or disrupting the target mRNAs. As regulators of post-transcriptional mRNA expression, miRNAs are widely dysregulated in a variety of tumours including ovarian cancer (He and Hannon, 2004; Hill and Tran, 2021). In our previous study, we found that the expression of miR-19a-3p was significantly increased in ovarian cancer tissues, and it could promote proliferation and invasion of ovarian cancer cells (Bai et al., 2019). In the present study, we further found that miR-19a-3p promotes aerobic glycolysis in ovarian cancer cells via IGFBP3/PI3K/AKT signalling. These findings may provide new insights into the development of novel methods for ovarian cancer diagnosis and treatment.

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Abbreviations: AKT – protein kinase B, ECAR – extracellular acidification, GLUT1 – glucose transporter type 1, GLUT3 – glucose transporter type 3, IGF – insulin-like growth factor, IGFBP3 – insulin-like growth factor binding-protein 3, LDHA – lactate dehydrogenase A, miR-19a-3p – microRNA-19a-3p, miRNA(s) – microRNA(s), OC – ovarian cancer, PI3K – phosphoinositide 3-kinase, PKM2 – pyruvate kinase isozyme type M2, qPCR – quantitative real-time PCR, RNAi – RNA interference, RT – reverse transcription, TCA – tricarboxylic acid cycle.

## Material and Methods

### Cell culture

Human normal ovarian epithelial cells (IOSE80) were purchased from Tianjin Saier Biotechnology (Tianjin, China) and cultured in RPMI-1640 medium (Hyclone, Logan, UT) supplemented with 10 % foetal bovine serum (FBS) (Hyclone), 100 units/ml penicillin, and 100 µg/ml streptomycin (Solarbio, Beijing, China). Ovarian cancer cell lines SKOV3 and ES-2 were cultured as previously described (Bai et al., 2019).

### Establishment of stable ovarian cancer cell lines

Lentiviral vectors expressing miR-19a-3p or insulin-like growth factor binding-protein 3 (IGFBP3) (LV-miR-19a-3p or LV-IGFBP3) and siRNAs for miR-19a-3p or IGFBP3 (LV-IGFBP3-RNAi or LV-IGFBP3-RNAi), and corresponding negative controls, respectively (LV-miR-19a-3p-NC or LV-IGFBP3-NC, LV-miR-19a-3p-inhibition-NC or LV-IGFBP3-RNAi-NC), were purchased from GeneChem (Shanghai, China). SKOV3 and ES-2 cells were infected with different lentiviruses for 72 h and selected with 1 µg/ml puromycin for three weeks (Bai et al., 2019).

### RNA isolation and RT-qPCR

A Total RNA Kit (TianGen, Beijing, China) was used to purify total RNA from the cell lines. mRNA reverse transcription (RT) and qPCR were performed using a PrimeScript™ RT reagent Kit (Takara, Beijing, China) and TB Green® Premix Ex Taq™ II (Takara), respectively. The primers were synthesized by Sangon Biotech (Shanghai, China) and the primer sequences are listed in Table 1. The expression of miRNA or mRNA was calculated by the  $2^{-\Delta\Delta CT}$  method, using U6 or  $\beta$ -actin, respectively, as an internal reference control for miRNA or gene expression assays.

### Western blots

Cells were lysed with pre-cooling lysis buffer for 30 min to extracted protein. After separation by SDS-PAGE, the protein was transferred to polyvinylidene difluoride (PVDF) membranes and blocked for 1.5 h at room temperature. The PVDF membranes were incubated at 4 °C overnight with indicated primary antibodies (Proteintech, Wuhan, China), including anti-IGFBP3, anti-AKT, anti-pAKT, anti-PKM2, anti-LDHA, anti-GLUT1, anti-GLUT3, and anti- $\beta$ -actin (loading control, Bioss, Beijing, China). After washing, the membranes were incubated with secondary antibody (Bioss) for 1.5 h at room temperature. The membranes were developed using the ECL kit (NCM Biotech, Suzhou, China) after washing. The target signals were quantified using Image-J software and normalized using  $\beta$ -actin.

### Analysis of ATP and lactate production

The Enhanced ATP Assay Kit (Beyotime, Shanghai, China) and colorimetric lactate kit (Solarbio) were used to examine ATP and lactate, respectively, according to the manufacturer's protocol. For ATP assays, renilla luminometer units (RLU) were read by a luminometer (PerkinElmer, Waltham, MA). For lactate assays, the absorbance at 570 nm was read by a multifunctional microplate reader at room temperature.

### Extracellular acidification rate (ECAR) assays

A Seahorse XF Glycolysis Stress Test Kit (Agilent, Santa Clara, CA) was used to measure the extracellular acidification rate (ECAR) of ovarian cancer cells, according to the manufacturer's instructions. In brief, SKOV3 and ES-2 ( $2 \times 10^4$ ) cells were seeded into XFe24 microplates. Before experiments, the cartridge sensor was hydrated overnight in a CO<sub>2</sub>-free incubator, cell culture medium was replaced, and cells were then incubated with assay medium for 1 h at 37 °C in a CO<sub>2</sub>-free incubator,

Table 1. The primer sequences for RT-qPCR

Gene	Sequence (5'→3')
miR-19a-3p	Forward: TGCGGTGTGCAAATCTATGCA Reverse: CCAGTGCAGGGTCCGAGGT RT: GTCGTATCCAGTGCAGGGTCCGAGGTGCACTGGATACGACTCAGTTTTGC
U6	Forward: TGCGGGTGTCTCGCTTCGGCAGC Reverse: CCAGTGCAGGGTCCGAGGT RT: GTCGTATCCAGTGCAGGGTCCGAGGTGCACTGGATACGACAAAATATGG
PKM2	Forward: ACTGGCATCATCTGTACCATTG Reverse: AGCCACATTCATTCCAGACTTA
LDHA	Forward: AGGTGATCAAACCTCAAAGGCTA Reverse: CCCAAAATGCAAGGAACACTAA
GLUT1	Forward: CTCCTGGTGATGCTTAGTGCCTTG Reverse: GCTGTTGTTCCGAGTGGGCAGTG
GLUT3	Forward: TTCAATGCTGATTGTCAACCTG Reverse: GCATTTCAACCGACTTAGCTAC
$\beta$ -actin	Forward: CCTGGCACCCAGCACAAT Reverse: GGGCCGGACTCGTCATAC

followed by sequential addition of glucose (100 mM), oligomycin (100  $\mu$ M) and 2-deoxyglucose (500 mM). All measurements were recorded at set time intervals. ECAR after oligomycin treatment indicates glycolytic capacity.

### *Statistical analysis*

All experiments were independently run at least three times. Statistical results were expressed as mean  $\pm$  SD and the data were analysed using SPSS 26.0 (IBM, Armonk, NY) with two-tailed Student's *t*-test. The *P* value  $<$  0.05 was considered statistically significant.

## **Results**

### *MiR-19a-3p promotes aerobic glycolysis in ovarian cancer cells*

Our previous study has shown that the expression of miR-19a-3p is up-regulated in ovarian cancer tissues (Bai et al., 2019). In this study, by RT-qPCR examination of miR-19a-3p expression, we found that the expression of miR-19a-3p was significantly higher in ES-2 and SKOV3 ovarian cancer cells as compared with that in normal ovarian cells IOSE80 (Fig. 1A). To understand the correlation between miR-19a-3p and aerobic glycolysis in ovarian cancer cells, we established ovarian cancer cells that stably over-express miR-19a-3p, or its expression is knocked down by a lentivirus containing green luciferase, and the efficiency of miR-19a-3p expression was measured by RT-qPCR (Fig. 1B–C). We found that over-expression of miR-19a-3p and knockdown of miR-19a-3p expression promotes and inhibits, respectively, ATP and lactate production in ovarian cancer cells (Fig. 1D–E). Hydrogen ions produced by aerobic glycolysis in tumour cells cause an acidic environment outside the cell, while the extracellular acidification rate (ECAR) can directly reflect the level of cellular glycolysis. Further examination of the glucose metabolism showed a significant increase in ECAR and maximal glucose metabolism capacity in ovarian cancer cells over-expressing miR-19a-3p, whereas down-regulation of miR-19a-3p expression inhibited ECAR and maximal glucose metabolism capacity (Fig. 1F–G), suggesting that miR-19a-3p promotes aerobic glycolysis in ovarian cancer cells.

### *MiR-19a-3p increases glycolytic gene expression in ovarian cancer cells*

PKM2 determines whether the glucose carbohydrates are degraded to pyruvate and lactate, or carbohydrates are transported to the synthetic process. LDHA controls the conversion between pyruvate and lactate. GLUT1 and GLUT3 are essential for the transportation of glucose into the cell. The expression of these molecules is altered in the process of aerobic glycolysis. Therefore, we evaluated the expression of PKM2, LDHA, GLUT1 and GLUT3 in ovarian cancer cells with miR-19a-3p

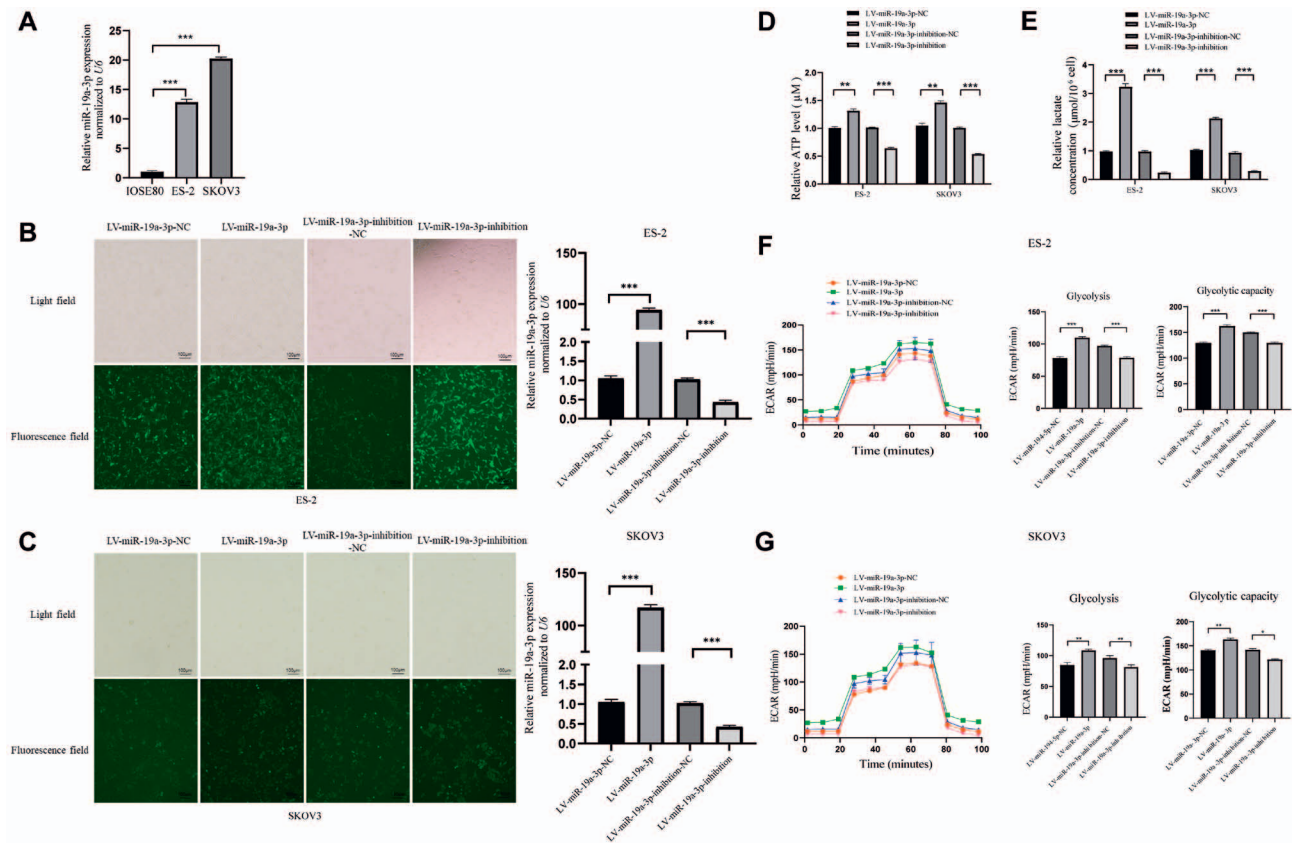
over-expression or knockdown, as measured by qPCR and Western blots. We observed that over-expression of miR-19a-3p increases the expression of PKM2, LDHA, GLUT1 and GLUT3, while knockdown of miR-19a-3p expression decreases the expression of these glycolytic genes at both mRNA (Fig. 2A–D) and protein levels (Fig. 2E–F) in ovarian cancer cells. Thus, these finding indicated that miR-19a-3p regulates expression of key molecules that are important in aerobic glycolysis.

### *IGFBP3 inhibits aerobic glycolysis in ovarian cancer cells*

We have previously found that IGFBP3 is a functional target of miR-19a-3p (Bai et al., 2019). Therefore, we examined the expression of IGFBP3 in ovarian cancer cells and normal ovarian epithelial cells by Western blot. The level of IGFBP3 protein in ES-2 and SKOV3 was significantly lower than that of IOSE80 cells (Fig. 3A). IGFBP3 was over-expressed or knocked down using lentivirus transduction in SKOV3 and ES-2 cells and lentiviruses carrying red luciferase. The over-expression or knockdown of IGFBP3 was successfully confirmed through the observation of red luciferase, and the expression level of IGFBP3 was determined by Western blots (Fig. 3B–C). By over-expression of IGFBP3 or knocked down IGFBP3 expression, we found that ATP production (Fig. 3D), lactate production (Fig. 3E), and ECAR levels (Fig. 3F) and glycolytic capacity (Fig. 3G) were decreased or increased, respectively, in ovarian cancer cells. In addition, we found that over-expression of IGFBP3 or knockdown of IGFBP3 expression suppresses or promotes, respectively, the expression of mRNA (Fig. 3H) and protein expression (Fig. 3I–J) of PKM2, LDHA, GLUT1 and GLUT3, suggesting that IGFBP3 suppresses ovarian cancer cell aerobic glycolysis.

### *MiR-19a-3p regulates aerobic glycolysis through IGFBP3 in ovarian cancer cells*

Considering that knockdown of IGFBP3 expression and over-expression of miR-19a-3p showed similar results in the regulation of aerobic glycolysis in ovarian cancer cells, we hypothesized that miR-19a-3p increases aerobic glycolysis through reduced expression of IGFBP3 in ovarian cancer cells. To prove that, we over-expressed IGFBP3 in ES-2 and SKOV3 cells with miR-19a-3p over-expression or knockdown and observed the green and red luciferase together to confirm the co-expression of IGFBP3 and miR-19a-3p in ovarian cancer cells (Fig. 4A–B). We found that over-expression of IGFBP3 counteracts the promotion of aerobic glycolysis including ATP production (Fig. 4C), lactate production (Fig. 4D), and ECAR levels (Fig. 4E) and glycolytic capability (Fig. 4F) by miR-19a-3p over-expression in ovarian cancer cells. Meanwhile, we found that the inhibition of ATP, lactate, ECAR and glycolytic capability caused by miR-19a-3p knocking down was signifi-



**Fig. 1.** MiR-19a-3p promotes aerobic glycolysis in ovarian cancer cells. (A) Quantification of miR-19a-3p expression in ovarian cancer cells. U6 was used as the internal control. (B–C) Fluorescence graph (100× magnification) and qPCR shows establishment of stable ovarian cell lines ES-2 (B) and SKOV3 (C) with over-expression of miR-19a-3p or knocked down miR-19a-3p expression. (D–G) Quantification of ATP level (D), lactate concentration (E), ECAR (F) and glycolytic capacity (G) in cells with miR-19a-3p over-expression or knockdown. \* $P < 0.05$ ; \*\* $P < 0.01$ , \*\*\* $P < 0.001$ . Each experiment was repeated thrice ( $N = 3$ ). ECAR: extracellular acidification rate; qPCR: quantitative polymerase chain reaction.

cantly counteracted by down-regulation of IGFBP3 expression (Fig. 4C–F).

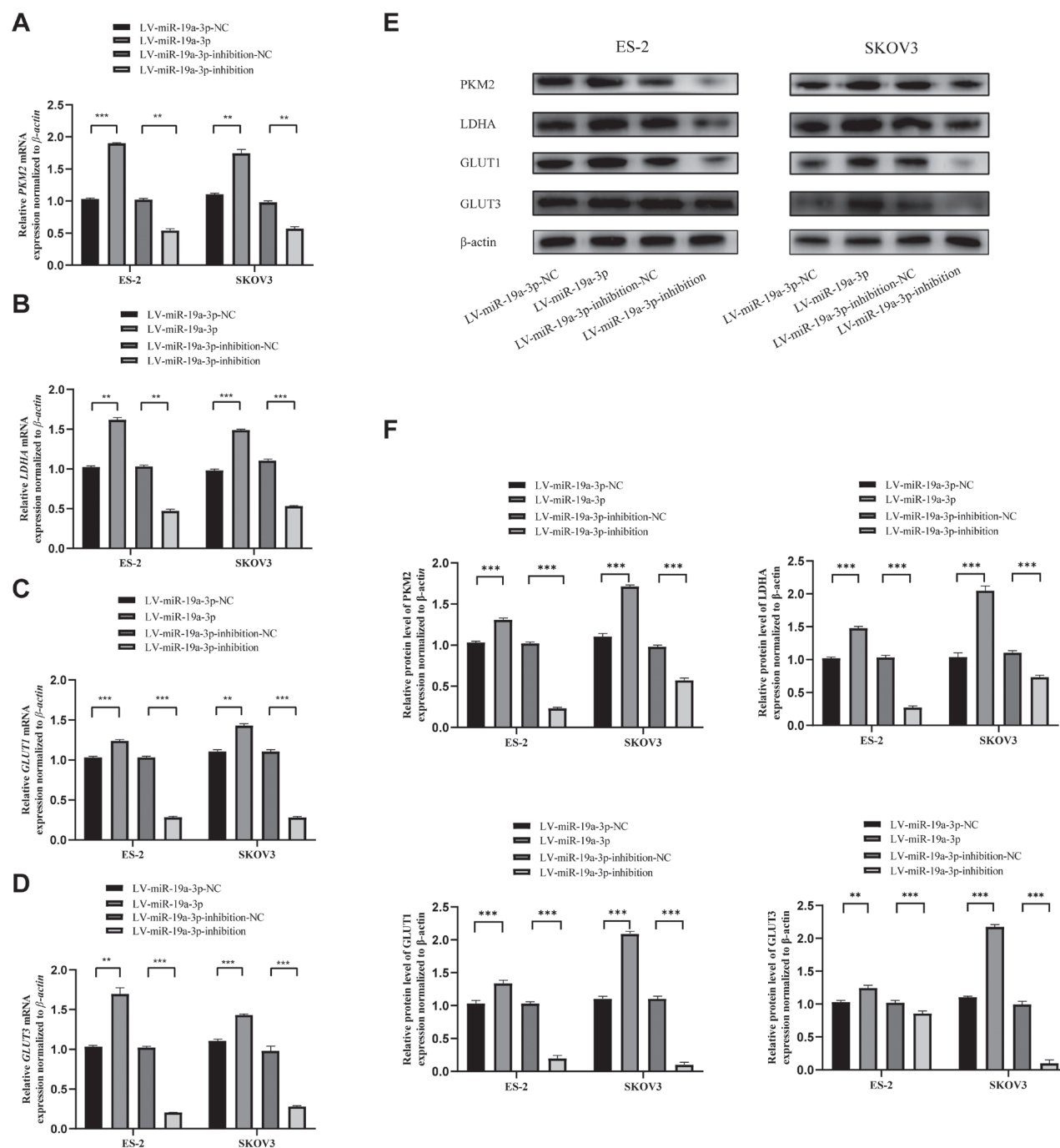
### *MiR-19a-3p regulates the IGFBP3/PI3K/AKT pathway in ovarian cancer cells*

IGFBPs can bind to insulin-like growth factor 1 (IGF-1) to inhibit its binding to IGFR, and therefore inhibit the activation of IGFR's downstream PI3K/AKT. In order to explore whether miR-19a-3p regulates aerobic glycolysis through the PI3K/AKT pathway in ovarian cancer cells, we detected the activation of AKT in SKOV3 and ES-2 cell lines. We found that AKT activation is decreased in ovarian cancer cells when IGFBP3 is over-expressed, and knockdown of IGFBP3 expression increases the AKT activation (Fig. 5A). Furthermore, we observed that miR-19a-3p over-expression promotes AKT activation, while knockdown of miR-19a-3p expression inhibits the AKT activation (Fig. 5B). In line with these results, the AKT activation caused by miR-19a-3p over-expression was counteracted by IGFBP3 over-expression, while knockdown of IGFBP3 expression rescued the inhibition of AKT activation by down-

regulation of miR-19a-3p expression in ovarian cancer cells (Fig. 5C). These results further suggested that miR-19a-3p increases the activation of the PI3K/AKT pathway by inhibiting IGFBP3 expression in SKOV3 and ES-2 cell lines. Taken together, these data showed that miR-19a-3p promotes aerobic glycolysis in ovarian cancer cells by targeting the IGFBP3/PI3K/AKT axis (Fig. 5D).

## Discussion

MiRNAs regulate the aerobic glycolysis in various tumour cells by interacting with key enzymes and cellular signalling pathways (Zhang et al., 2022). It has been shown that miR-383 down-regulates the expression level of lactate dehydrogenase A (LDHA) in ovarian cancer cells, thereby inhibiting glycolysis (Han et al., 2017). MiR-203 promotes aerobic glycolysis in ovarian cancer cells by directly targeting pyruvate dehydrogenase B (PDHB) (Xiaohong et al., 2016). MiR-603 over-expression can inhibit aerobic glycolysis in ovarian cancer cells through directly targeting hexokinase 2 (HK2) (Lu et al., 2019). Our research found that miR-19a-3p

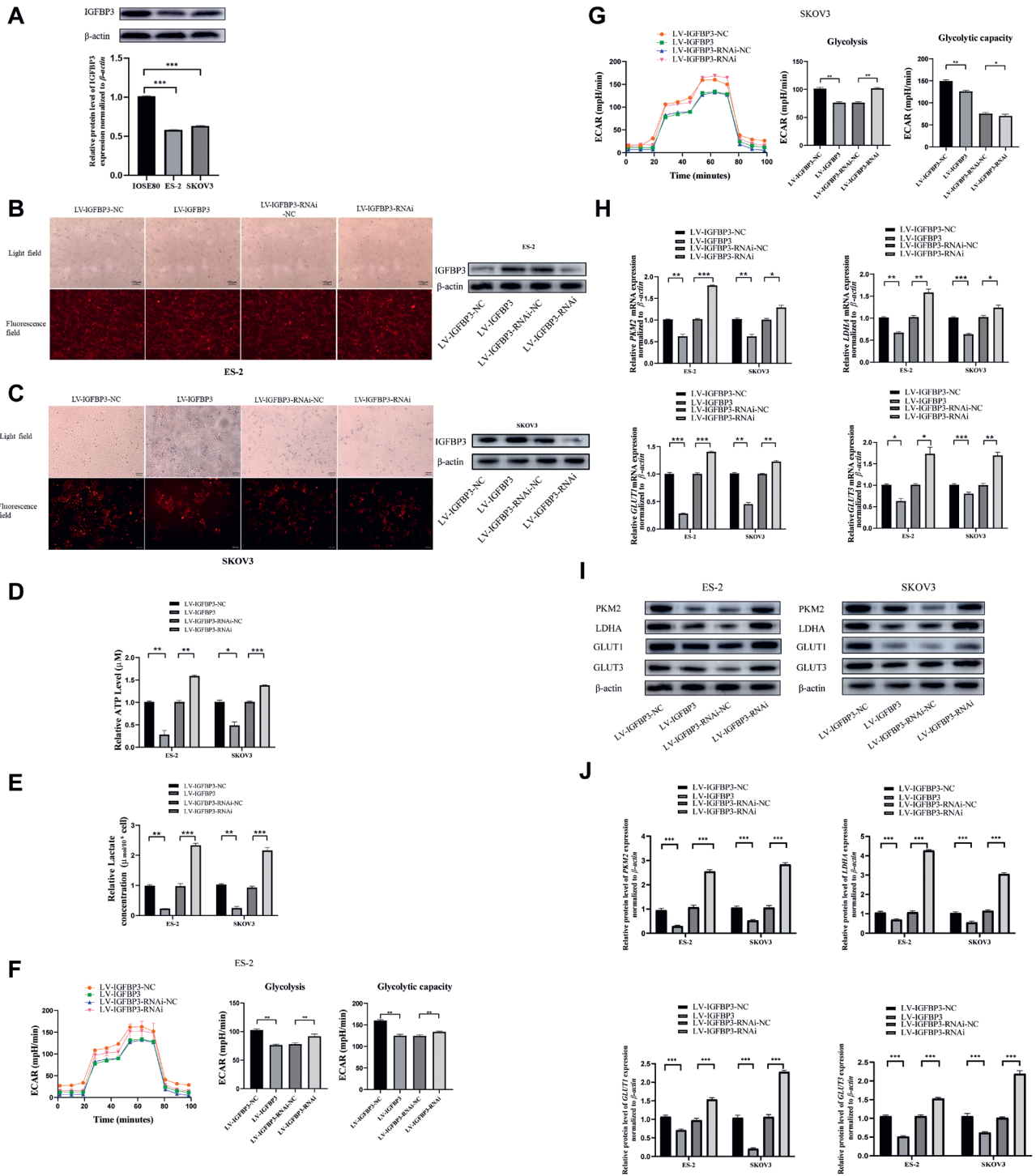


**Fig. 2.** MiR-19a-3p increases glycolytic gene expression in ovarian cancer cells. (A–D). mRNA expression of PKM2 (A), LDHA (B), GLUT1 (C) and GLUT3 (D) in ovarian cancer cells with miR-19a-3p over-expression or knockdown by qPCR analysis, using  $\beta$ -actin as an internal control. (E–F). Western blot images (E) and statistical analysis (F) show the protein expression of PKM2, LDHA, GLUT1 and GLUT3 in miR-19a-3p over-expressing or knocked down ES-2 and SKOV3 cells.  $\beta$ -Actin served as an internal control. \* $P < 0.05$ ; \*\* $P < 0.01$ , \*\*\* $P < 0.001$ . Each experiment was done thrice (N = 3). PKM2: pyruvate kinase M2; LDHA: lactate dehydrogenase A; GLUT: glucose transporter.

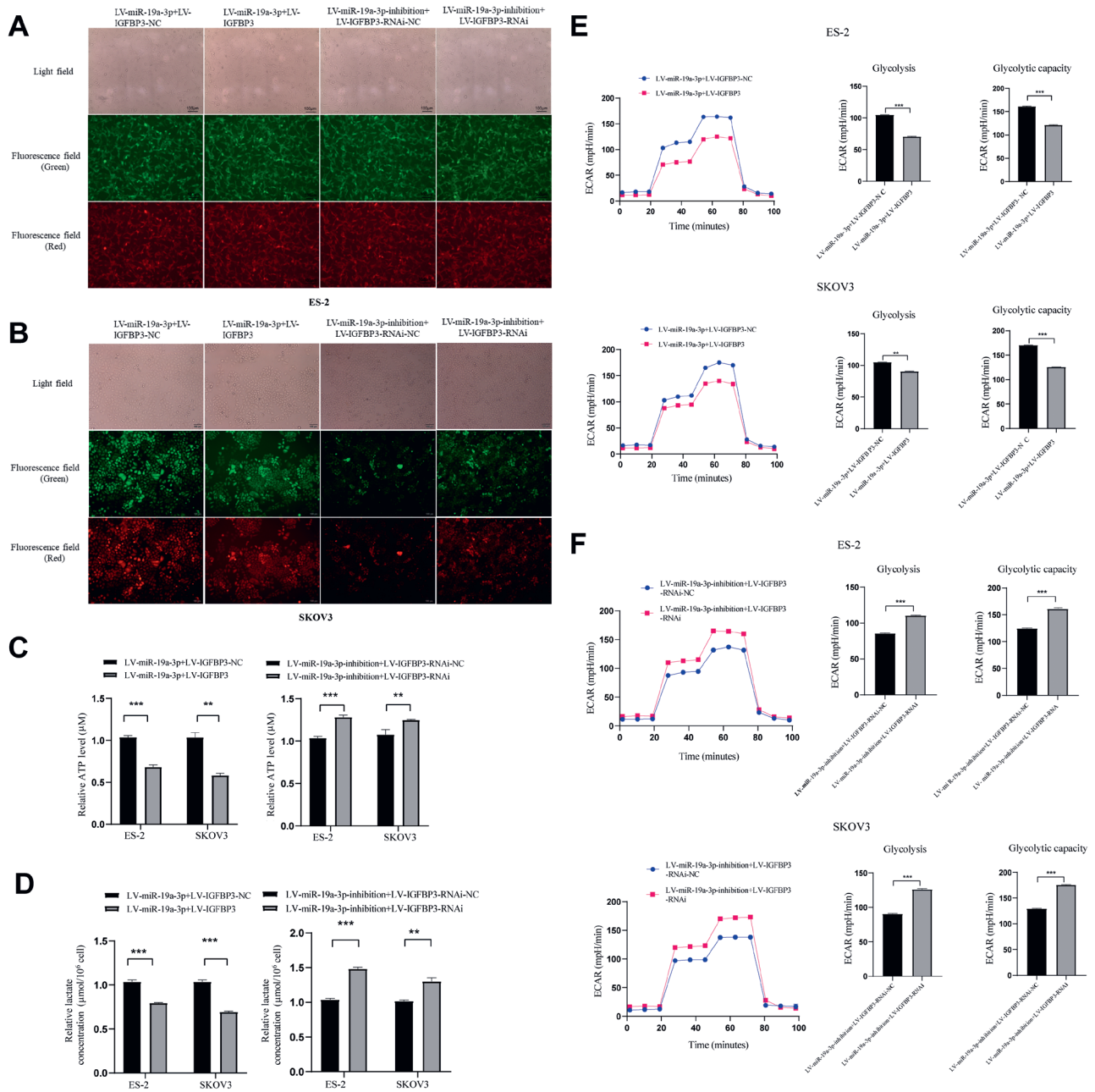
increases the expression of PKM2, LDHA and glucose transporter proteins GLUT1 and GLUT3, which in turn enhances the Warburg effect in SKOV3 and ES-2 cell lines, while inhibition of miR-19a-3p expression attenuated aerobic glycolysis, suggesting that miR-19a-3p is an important deriving factor for reprogramming glyco-

lysis in ovarian cancer cells. Rescue assays proved the promotive function of miR-19a-3p in aerobic glycolysis in ovarian cancer cells by targeting IGFBP3.

The function of miRNAs depends on targeting and regulating the expression of target genes. In our previous study, IGFBP3 was identified as a direct and functional



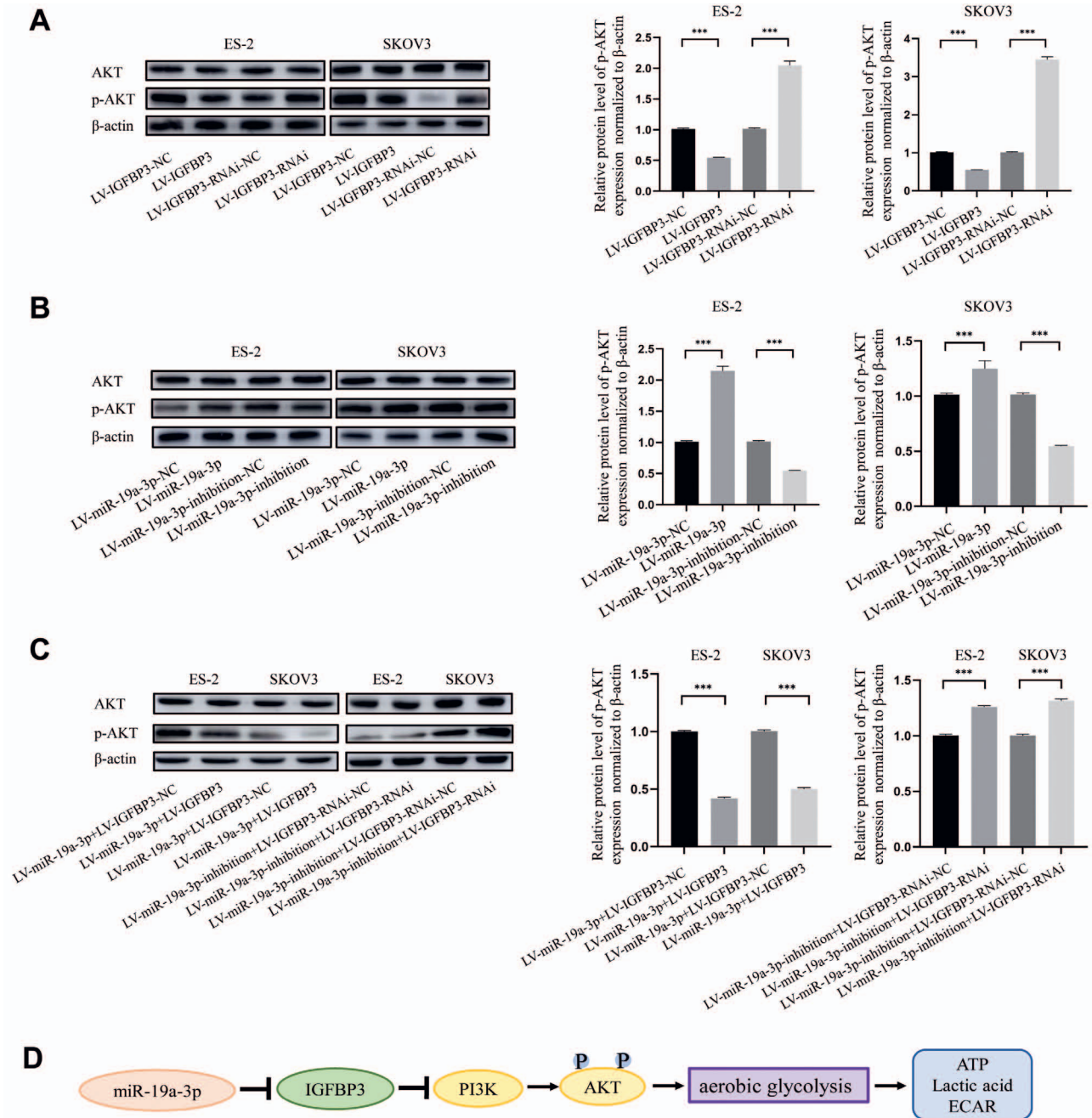
**Fig. 3.** IGFBP3 inhibits aerobic glycolysis in ovarian cancer cells. **(A)** IGFBP3 expression in ovarian cancer cells by Western blot analysis. **(B–C)** Fluorescence graph (100× magnification) and Western blot show the establishment of stable ovarian cell lines ES-2 **(B)** and SKOV3 **(C)** with over-expression of IGFBP3 or knockdown of IGFBP3 expression. **(D–G)** Quantification of ATP level **(D)**, lactate concentration **(E)**, ECAR **(F)** and glycolytic capacity **(G)** in ES-2 and SKOV3 cells with IGFBP3 over-expression or knockdown. **(H)** mRNA expression of PKM2, LDH, GLUT1, GLUT3 in ovarian cancer cells with IGFBP3 over-expression or knockdown by qPCR analysis. β-Actin served as an internal control. **(I–J)** Western blot images **(I)** and quantitative analysis **(J)** of PKM2, LDH, GLUT1, GLUT3 protein expression in ovarian cancer cells with IGFBP3 over-expression or knockdown, using β-actin as a loading control. \*P < 0.05; \*\*P < 0.01, \*\*\*P < 0.001. Each experiment was done thrice (N = 3).



**Fig. 4.** MiR-19a-3p regulates aerobic glycolysis through IGFBP3 in ovarian cancer cells. (A–B) Fluorescence graph (100× magnification) of ES-2 (A) and SKOV3 (B) cells infected with a lentivirus with miR-19a-3p over-expression or knock-down (green fluorescence), along with a lentivirus with IGFBP3 up-regulation or down-regulation (red fluorescence), respectively. (C–F) Quantification of ATP level (C), lactate concentration (D), ECAR (E) and glycolytic capacity (F). \* $P < 0.05$ ; \*\* $P < 0.01$ , \*\*\* $P < 0.001$ . Each experiment was done thrice ( $N = 3$ ).

target gene of miR-19a-3p (Bai et al., 2019). IGFBP3 is the most abundant IGF-binding protein in the circulation and is one of the important carriers of IGF (Jogie-Brahim et al., 2009). Recent research has confirmed that IGFBP3 acts as a key regulator in tumour development and progression. In glioma cells, low expression of IGFBP3 induces apoptosis and DNA damage, thereby inhibiting tumour growth (Chen et al., 2019). In the serum of colon cancer patients, IGFBP3 expression is

down-regulated and positively correlates with poorer clinical prognosis (Hou et al., 2019). Transforming growth factor  $\beta$  (TGF- $\beta$ ) activates IGFBP3, which in turn promotes the migration and invasion of colon cancer cells (Navarro et al., 2020). The expression level of IGFBP3 is significantly increased and promotes brain metastasis in lung adenocarcinoma cells (Yang et al., 2019). In contrast to the anti-tumour role of IGFBP3, some studies suggest that IGFBP3 might be a tumour



**Fig. 5.** MiR-19a-3p regulates the IGFBP3/PI3K/AKT pathway in ovarian cancer cells. **(A)** Western blot images and quantitative analysis of AKT and p-AKT in ES-2 and SKOV3 cells with over-expressed or knocked down IGFBP3. **(B)** Examination of AKT and p-AKT in ES-2 and SKOV3 cells with miR-19a-3p over-expression or knockdown by Western blot. **(C)** Proteins AKT and p-AKT were examined by Western blot in ES-2 and SKOV3 cells with over-expression or knockdown of miR-19a-3p, along with over-expression or knockdown of IGFBP3.  $\beta$ -Actin served as a loading control. \* $P < 0.05$ ; \*\* $P < 0.01$ , \*\*\* $P < 0.001$ . Each experiment was done thrice ( $N = 3$ ). **(D)** Schematic diagram of the regulation of aerobic glycolysis by miR-19a-3p in ovarian cancer cells.

promoter, depending on the cellular environments (Jin et al., 2020). In this study, we found that IGFBP3 inhibits aerobic glycolysis in ovarian cancer cells. We further found that down-regulation of IGFBP3 promotes the activation of the PI3K/AKT signalling pathway, which is downstream of the type 1 IGF receptor (IGF1R)

system. The PI3K/AKT signalling pathway regulates protein biosynthesis, cell growth, migration, drug resistance (Tian et al., 2023), and it is closely linked to glucose metabolism in tumour cells (Wang et al., 2017; Park et al., 2020). Research has found that the PI3K/AKT pathway promotes metabolic reprogramming by regu-



lating glycolytic enzymes to enhance the expression of glycolysis-related genes (Bonelli et al., 2020). These enzymes such as PKM2 can promote the proliferation of osteosarcoma (Shen et al., 2019), lung cancer (Lin et al., 2021), pancreatic cancer (Cai et al., 2022) and gastric cancer (Li et al., 2019a, c) cells by direct or indirect participation in the regulation of gene expression in the glycolysis pathway (Zhang et al., 2021). It has been reported that CD36 promotes the growth and metastasis of hepatocellular carcinoma cells by regulating the aerobic glycolysis in cells through the PI3K/AKT signalling pathway (Luo et al., 2021). In colorectal cancer cells, the activation of the PI3K/AKT signalling pathway leads to up-regulation of hypoxia-inducible factor 1 $\alpha$  (HIF-1 $\alpha$ ), which promotes aerobic glycolysis and allows tumour cells to acquire drug resistance (Dong et al., 2022). Vitamin K2 enhances glucose consumption and lactic acid production by PI3K/AKT and HIF-1 $\alpha$  to promote glycolysis in bladder cancer cells, reduce synthesis of acetyl coenzyme A and inhibit the TCA cycle (Duan, 2020). Copine-1 (CPNE1) promotes the proliferation and aerobic glycolysis of colorectal cancer cells by activating the AKT-GLUT1/HK2 signalling pathway (Wang et al., 2021). It was shown that activated AKT promotes the accumulation of GLUT1 on the cell membrane and glucose uptake by cells, which in turn promotes aerobic glycolysis in tumour cells (Hosios and Manning, 2021). In the present study, we found that miR-19a-3p enhances the activation of the PI3K/AKT pathway by suppressed expression of IGFBP3 in ovarian cancer cells. Further studies are needed to identify the potential roles of miR-19a-3p in the energy metabolism of ovarian cancer that are meaningful in the pathogenesis and therapy of ovarian cancer.

Taken together, our findings reveal that miR-19a-3p is a critical regulator for promoting aerobic glycolysis in ovarian cancer cells. It targets and down-regulates the expression of IGFBP3, which in turn increases the activation of the PI3K/AKT signalling pathway, providing a new insight into the possible application of miR-19a-3p in the treatment of ovarian cancer.

## Conclusion

MiR-19a-3p mediated targeting of the IGFBP3/PI3K/AKT axis that promotes aerobic glycolysis in ovarian cancer cells. MiR-19a-3p has a potential to become a novel therapeutic target of ovarian cancer.

## Conflicts of interest

The authors declare that they have no conflicts of interest.

## Authors' contributions

Author contribution: study conception and design: Ru Bai, data collection: Lijun Du, Kaikai Dou, Dan Zhang, Nianhai Liang, Huidong Xia, Ningping Wang, analysis and interpretation of results: Lijun Du, draft manuscript preparation: Lijun Du, Ru Bai, Jianmin Sun.

## Availability of data and materials

All data of this work can be obtained from the corresponding authors by reasonable request.

## Ethics approval

This study was approved by the Ethical Committee of Ningxia Medical University (Protocol Number: 2021-N0024).

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