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Research

Overexpression of MAFG-AS1 in ovarian cancer promotes glucose metabolism reprogramming and malignant biological behavior of ovarian cancer cells by regulating HIF-1α

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Received: 13 October 2024 / Accepted: 18 April 2025
Published online: 15 May 2025

Abstract

Objective This research explored the involvement of MAFG-AS1 in metabolic reprogramming and potential molecular mechanisms in ovarian cancer (OC).

Methods The ability of MAFG-AS1 silencing to affect the glucose intake, lactate production, ECAR, OCR and ATP concentrations and NAD^+/NADH ratios in OC cells was examined. Cell cycle phases and apoptosis were measured by flow cytometry. The influences of MAFG-AS1overexprssion on the above assays were also identified.

Results A transient reduction in the number of SKOV3 and HO8910 cells in the MAFG-AS1 knockdown group. MAFG-AS1 knockdown can inhibit cell proliferation, induce apoptosis, and enhance the number of cells in G2 phase. Silencing MAFG-AS1 can inhibit the glucose uptake rate, extracellular lactate production, and ECAR of OC cells, ATP levels, and can promote OCR and NAD^+/ NADH ratio oxidative phosphorylation. Silencing MAFG-AS1 can inhibit HIF-1α in OC.

Conclusion Our study revealed silencing MAFG-AS1 could inhibit the proliferation and induce apoptosis of OC cells by inhibiting the HIF-1α-mediated glycolysis process. Therefore, this study further potentially reveals the machinery of MAFG-AS1 in regulating OC cell proliferation and apoptosis, which is expected to provide a theoretical basis for the study of new targets.

Keywords MAFG-AS1 expression · Glucose metabolism reprogramming · Ovarian cancer · Cell proliferation/growth

1 Introduction

Ovarian cancer (OC) is the commonest type of gynecological neoplasms, with approximately 238,719 new OC cases diagnosed worldwide each year, second only to cervical and endometrial cancers in terms of incidence [1]. The standard treatment for OC is placing it fifth in global tumor mortality and first in gynecological tumors [2, 3]. The high mortality rate of OC is explained by the absence of specific symptoms in the early stages of OC and the challenge of early screening. Approximately 70% of OC sufferers are already at stage III-IV at the diagnosis and have extensive pelvic and abdominal implant metastases and ascites formation, as well as a significant proportion of patients who develop resistance and recurrence after chemotherapy [4]. Therefore, uncovering and finding important biomarkers are important for improving the early diagnosis and treatment of OC as well as predicting and monitoring the progression of cancer.

Liu Jia and Fei Yu contributed equally to this work and share joint first authorship.

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It is well-known that malignant cells can promote tumor growth through their energy metabolism [5, 6]. In normoxic environments, malignant cells remain able to modify on their glucose metabolism through increased glycolysis to favor a malignant course of action, an effect referred to as the "Warburg effect" [7–9].

HIF-1α has a very important role in tumor growth, angiogenesis, proliferation, motility, invasion, and metastasis [10]. Previous evidence has confirmed that HIF-1α upregulation in cancer cells inhibited the Warburg effect, enhanced mitochondrial oxidative phosphorylation, and contributed to tumor cell apoptosis [11]. Additionally, glycolysis is mediated through activation of HIF-1α and stimulation of glycolytic enzymes. HIF-1α is a major regulator and essential for malignantly metabolic reprogramming [12]. HIF-1α is commonly found as an important regulator of glycolysis [13], which is very susceptible to rapid degradation, being stably expressed in immersing hypoxic conditions only [14].

LncRNAs are up-and-coming modulators participating in genetic expression, a variety of biological and geo-pathological events [15, 16]. Growing evidence has demonstrated that lncRNAs perform sophisticated and precisely regulated duties in carcinogenesis and progression by serving as either oncogenes or neoplastic repressors [17, 18]. They can not only manage the multiplication, or differentiation, aggression, and migration of oncogenic cells, but also modulate the metabolic re-programming of carcinoma cells [19, 20]. Besides, an increasing amount of data indicates that lncRNAs exert an essential functioning role in mediating the metabolism-related sequence of genes in terms of their transcription and translation, eventually resulting in carcinoma metabolic reprogramming [21, 22]. Alternatively, the latest findings from our group and others also indicated that lncRNAs facilitate energy metabolism and malignant behaviors via post-translational modifications of critical metabolism-linked protein factors [23–25]. The MAF bZIP transcription factor G-antisense RNA 1 (MAFG-AS1) is located on chromosome 17, which has been discovered as a novel oncogenic lncRNA for several years [26]. MAFG-AS1 accelerates colorectal cancer cell multiplication and aggression by aiming at NDUFA4 [27]. Moreover, MAFG-AS1 is a de novo clinically functional biomarker for advancement and worse consequences in gastrointestinal carcinomas [28]. In contrast, the role of MAFG-AS1 in glucose metabolism reprogramming and malignant behaviors of OC and the relationship with HIF-1 remain unreported.

2 Methods

2.1 Cell culture

SKOV3 and HO8910 cell lines were placed in RPMI-1640 medium (R8758, Sigma, USA) plus with 10% fetal bovine serum (12103C, Sigma) and 1% penicillin and streptomycin (P7539, Sigma) and placed in a constant humidity and constant temperature incubator (37 °C, 5% CO_2) for the cells to grow and adhere to the wall, and the culture solution needed to be changed every 48 h.

2.2 Plasmids and cell transfection

The siRNA-mediated knockdown of MAFG-AS1 (si-MAFG-AS1) and negative control (si-NC) were provided by GeneCopoeia Biotechnology Co., Ltd.(USA). For cell transfection, a total of $0.5–1.0 \times 10^5$ cells packed into 0.5 mL of complete growth medium were seeded in a 24-well plate and cultured for overnight. When reaching roughly 80%, the si-MAFG-AS1 or si-NC was transfected into SKOV3 and HO8910 cells by using the Lipofectamine™ 2000 (11,688–030, Thermo Fisher, USA). 6 h later, the medium containing transfection reagent refreshed with complete growth medium. After the next 48-h incubations, the cells were assayed for transgene expression.

2.3 CCK-8 assay

The cell propagation test was conducted in accordance with the description of the CCK-8 kit (AMJ-KT0001, EnzoLife Sciences, USA). Cells were prepared for seeding into 96-well plate at 5×10^3 /well. Subsequent to the seeding, 10 µL CCK-8 solution was mixed with 90 µL RPMI-1640 medium for 3 h incubations.

2.4 PCR assay

RNA was obtained from each group and then the concentration of RNA was determined. Genomic DNA was removed for reverse transcription reactions. Primer sequences for the MAFG-AS1 gene were searched on Primer-bank and primers were compared in Pubmed to determine their specificity, and primers were synthesized by Changsha Prime Tech Biotechnology. Primer sequences for the target gene and internal reference were as follows: MAFG-AS1: forward 5′-CGTTCTTAGTTGGTGGAGCG-3′and reverse 5′-CCGGACATCTAAGGGCAT CA-3′; GAPDH: forward 5′-AATGGATTTGGA CGCATTGGT-3′, and reverse 5′-TTTGCACTGGTACGTGTTG AT-3′.

2.5 Cell cycle assay

SKOV3 and HO8910 cells were cultivated in 12-well plates, with each well containing 1×10^6 cells. The MAFG-AS1 silencing or control cells were prepared. Subsequently, after a 24-h incubation period, the cells were treated with a cell cycle assay kit (CCS012, Multisciences, Hangzhou, China) following the manufacturer's instructions. FACS experiment was then conducted to analyze the cell cycle. We gated the target cell population in FSC-A/SSC-A to exclude debris, and then used FSC-H/FSC-A gate to eliminate doublets and ensure single-cell analysis. After propidium iodide (PI) staining, acquire DNA content signals in the appropriate fluorescence channel PI. FL2-W/FL2-A was applied to further exclude remaining aggregates and ensure accurate DNA quantification. Then, a histogram of PI fluorescence intensity (FL2-A) for the single-cell population was obtained. A flowJo software was used analyze the cell cycle phases.

2.6 Annexin V (AV)/ PI assay

The Annexin V-FITC/PI Apoptosis Detection Kit (BMS500FI-300, Thermo Fisher) was employed to detect cell apoptosis. The cells were resuspended in 100 µL binding buffer and then incubated with 5 µL Annexin V and 5 µL PI for 15 min at room temperature. Apoptotic cells were analyzed by a FACS Calibur flow cytometer (BD Biosciences).

2.7 Caspase-3 activity dectction

A caspase-3 activity fluorescent assay kit (169,639, Enzo Life Sciences) was employed following the manufacturer's recommended protocol. Transfected cells were seeded into 96-well plates at a density of 1×10^5 cells per well. Following experimental treatments, the caspase-3 activity was assessed according to the manufacturer's recommended protocol.

2.8 Measurement of glucose uptake and lactate production

Cells treated in different groupings were routinely digested and centrifuged, resuspended, and mixed by repeated pipetting with a pipette gun. Glucose uptake (KA4086, Abnova, USA). and lactate production (KA0833, Abnova) in the different subgroups were then checked using kits according to their instructions.

2.9 Extracellular acidification and oxygen consumption rate determination

The ECAR and OCR of cells were measured using a Seahorse XFe^{96} Cell Extracellular Flux Analyzer (Seahorse Bioscience, USA). The ECAR and OCR were measured using Seahorse XF Glycolytic Stress (102,194–100) /Mitochondrial Stress Kits (701,170–96), respectively. All process of test were undertaken following the Product Brochure.

2.10 ATP determination

ATP was measured using the ATP Analysis Kit (S0026, Byotime, China) according to the manufacturer's instructions. Treated cells were lysed in ice-cold ATP release buffer and centrifuged at 11,000 g for 10 min. In a 96-well plate (protected

from light), 100 µL of each supernatant or standard solution was mixed with 100 µL of ATP assay working dilution. Measurements were performed by a dual luciferase reporter gene assay system (Promega).

2.11 Statistical calculations

All data results are expressed as mean ± standard deviation (SD). Statistical correlations were analyzed using SPSS 27.0 software, and the comparison between two groups were analyzed using students' t-test. The potential correlation between the two variables was analyzed by Spearman's rank test. p-values < 0.05 were considered statistically significant.

3 Results

3.1 MAFG-AS1 expression in SKOV3 and HO8910 cells under diverse status

We firstly determined the expressions of MAFG-AS1 in SKOV3 (Fig. 1a) and HO8910 (Fig. 1b) cells after overexpression and knockdown of MAFG-AS1. The results demonstrated that the overexpression and knockdown transfection efficiency in SKOV3 and HO8910 cells was effective.

3.2 Silencing MAFG-AS1 suppressed proliferation and induced apoptosis in ovarian cancer cells

In our CCK-8 assay to detect cell proliferation, a transient decrease in the number of SKOV3 and HO8910 cells in MAFG-AS1 knockdown group (Fig. 2a and b). Next, flow cytometry was used to analyze cell cycle distribution, and it was found that MAFG-AS1 knockdown increased the amount of SKOV3 and HO8910 cells in G2 phase (Fig. 2c and d). We also found that MAFG-AS1 knockdown promoted the apoptosis of SKOV3 and HO8910 cells (Fig. 2e and f). Consistently, MAFG-AS1 silencing enhanced caspase-3 activity in SKOV3 and HO8910 cells (Fig. 2g). The above data suggest that MAFG-AS1 knockdown can inhibit cell proliferation and induce apoptosis.

3.3 Silencing MAFG-AS1 suppressed glucose consumption/ lactate production and promoted NAD^+ /NADH

Glycolysis and oxidative phosphorylation provide energy for tumor cells and glycolysis could promote tumor growth. In order to understand whether MAFG-AS1 could promote glycolysis, we examined glucose consumption and lactate production in OC cells after silencing MAFG-AS1. It was found that inhibition of MAFG-AS1 significantly reduced glucose consumption and lactate production (Fig. 3a and b). As oxidative phosphorylation enabled electron transfer through the conversion of NAD^+ and NADH, resulting in the generation of ATP. For this purpose, NADH levels were examined in OC cells after silencing MAFG-AS1. Silencing MAFG-AS1 in SKOV3 and HO8910 cells was found to decrease intracellular NADH levels and significantly increase the NAD^+/NADH ratio (Fig. 3c), and increase intracellular ATP content (Fig. 3d). All the above results could be partially reversed by MAFG-AS1 overexpression, suggesting that MAFG-AS1 contributed a role in the reprogramming of glycolytic metabolisms.

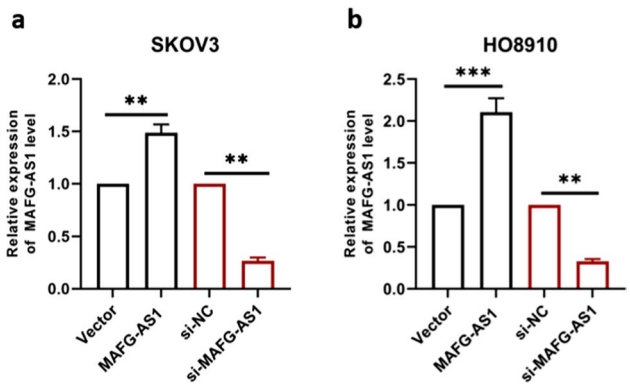

Fig. 1 The relative expression of MAFG-AS1 under diverse status in (**a**) SKOV3 and (**b**) HO8910 cell lines was measured by qPCR

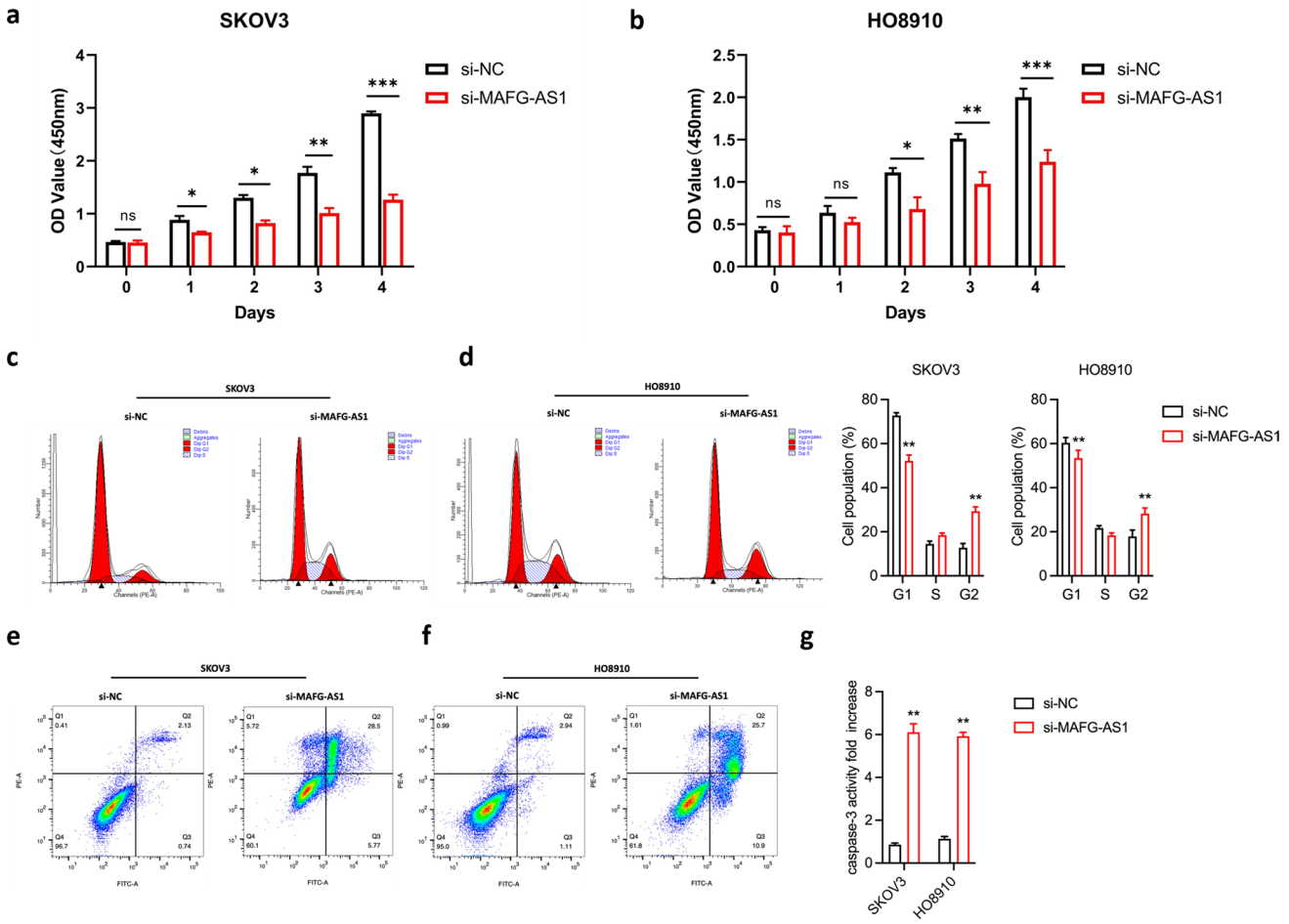

Fig. 2 The cell growth is detected with CCK-8 tests in (**a**) SKOV3 and (**b**) HO8910 cell lines after incubation for 0, 1, 2, 3, and 4 days. The flow cytometry assay was performed to analyze cell cycle distribution in (**c**) SKOV3 and (**d**) HO8910 cells after incubation for 24 h. The Annexin V-FITC/PI Apoptosis Detection Kit was used to detect apoptosis in (**e**) SKOV3 and (**f**) HO8910 cells after incubation for 24 h. A caspase-3 activity assay kit was used to measure caspase-3 activity in SKOV3 and HO8910 cells (**g**) after incubation for 24 h

3.4 Silencing MAFG-AS1 suppressed glycolysis and enhanced oxidative phosphorylation

Detection of extracellular acidification rates showed that knockdown of MAFG-AS1 could inhibit glycolytic capacity; glycolysis can be further enhanced when MAFG-AS1 was overexpressed (Fig. 4 a and b). In addition, intracellular OCR data showed that knockdown of MAFG-AS1 in SKOV3 and HO8910 cells significantly enhanced their oxidative phosphorylation; whereas high expression of MAFG-AS1 attenuated the oxidative phosphorylation capacity (Fig. 4c and d).

3.5 MAFG-AS1 could mediate HIF-1α, a key enzyme of glycolysis in ovarian cancer

Studies have demonstrated that HIF-1α is a major regulator of glycolysis and represents a key regulator of glycolytic reprogramming. The bio-informative result show that alterations of MAFG-AS1 in ovarian cancer samples influence HIF-1α (Fig. 5).

To verify whether the potential mechanism of silencing the effect of MAFG-AS1 on metabolic reprogramming in ovarian cancer was associated with HIF-1α, we determined the relative levels of HIF-1α in different groups of ovarian cancer cells by HIF-1α assay kits (Fig. 6a). The silencing of MAFG-AS1 reduced the level of HIF-1α expression in SKOV3 and HO8910 cells. Subsequent MAFG-AS1 overexpression results were also found to elevate HIF-1α expression (Fig. 6b). Taken together, we suggest that MAFG-AS1 is involved in the glycolytic reprogramming process in ovarian cancer.

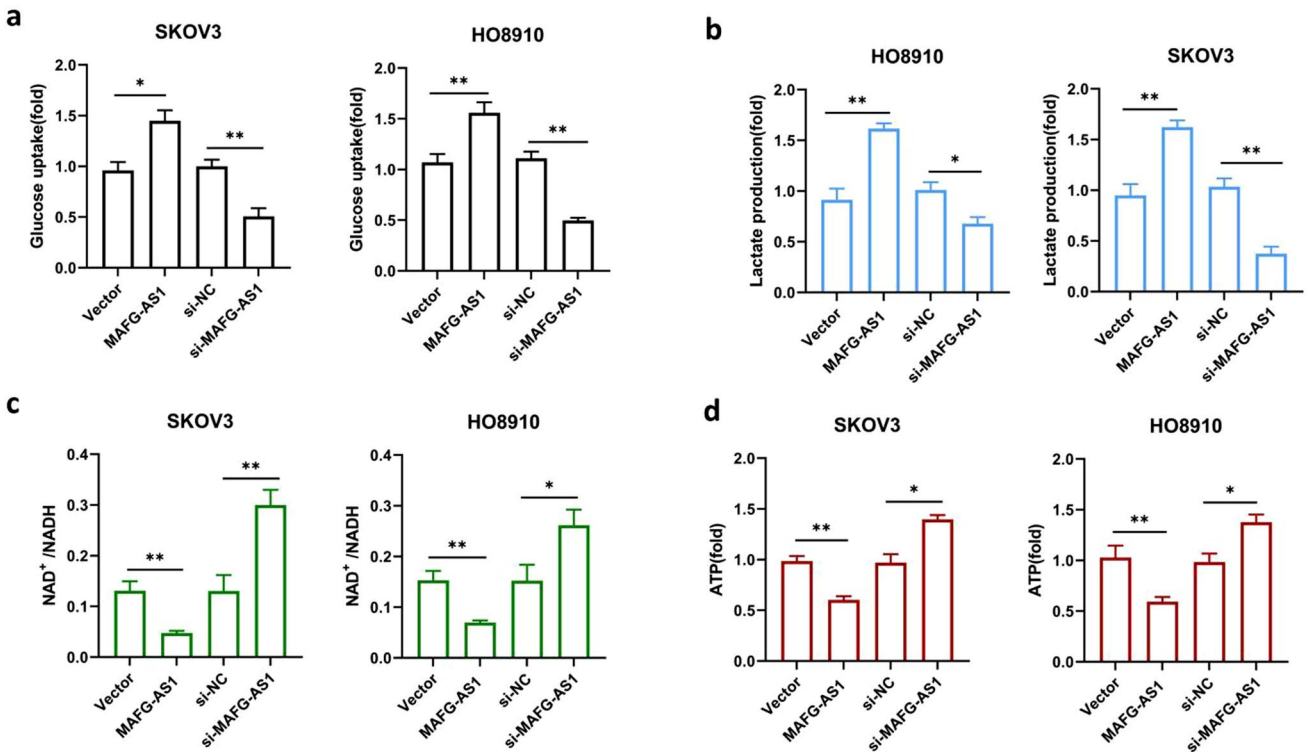

Fig. 3 (**a**) Glucose uptake was detected after cell transfection; (**b**) Lactate production was detected; (**c**) The ratio of NAD^+/NADH in cells were measured; (**d**) ATP levels were monitored after transfection

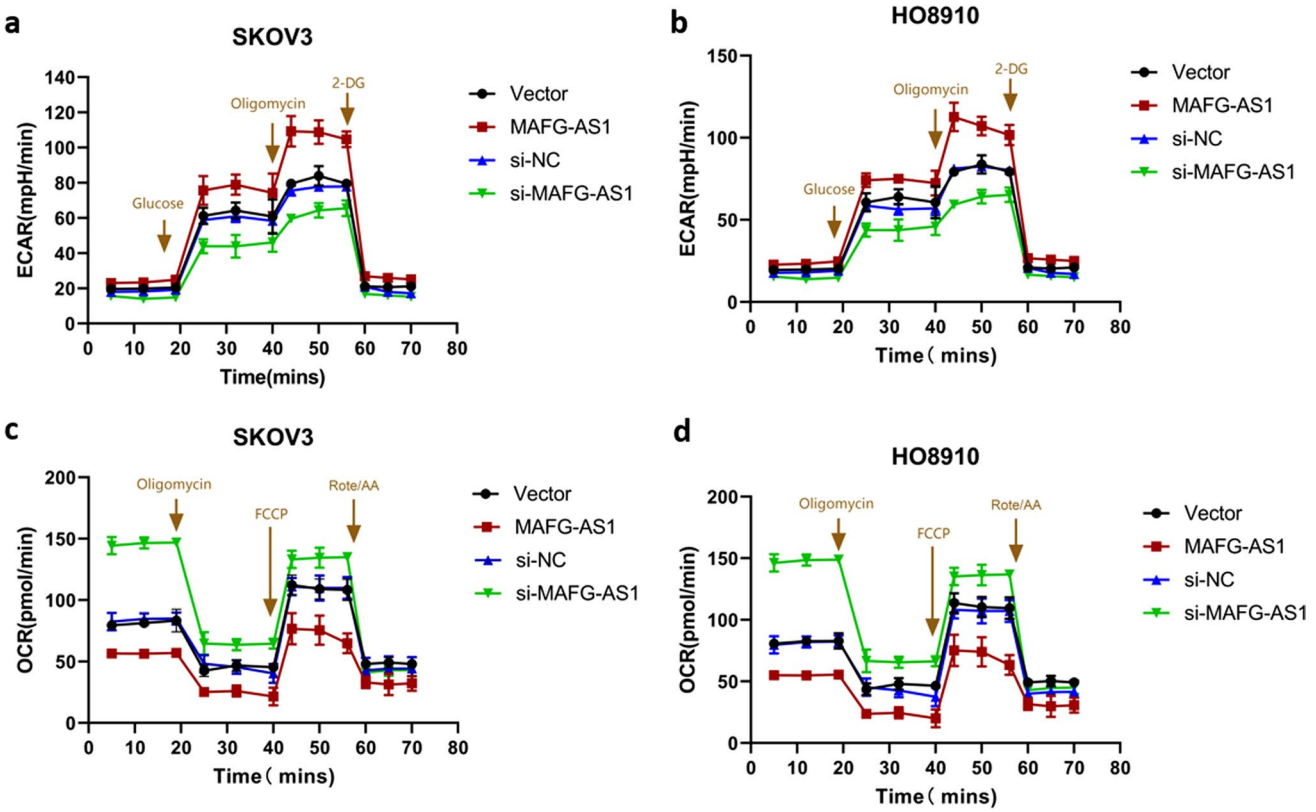

Fig. 4 (**a**, **b**) Glycolysis measured by ECAR in SKOV3 and HO8910 cells; (**c**, **d**) Detection of oxygen consumption rates in SKOV3 and HO8910 cells

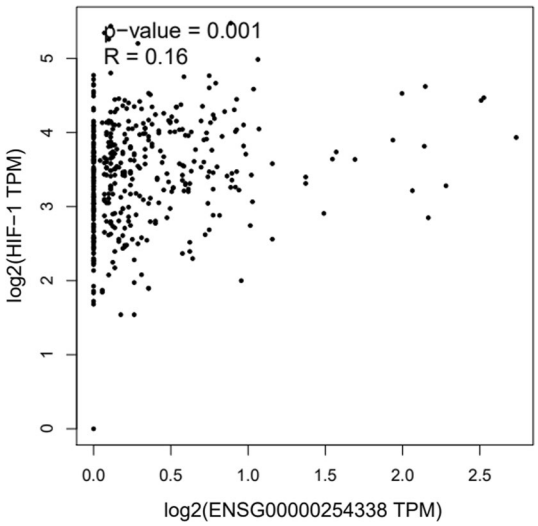

Fig. 5 The relationship between *HIF-1* gene and lncRNA MAFG-AS1 in ovarian cancer cases from the online database GEPIA2

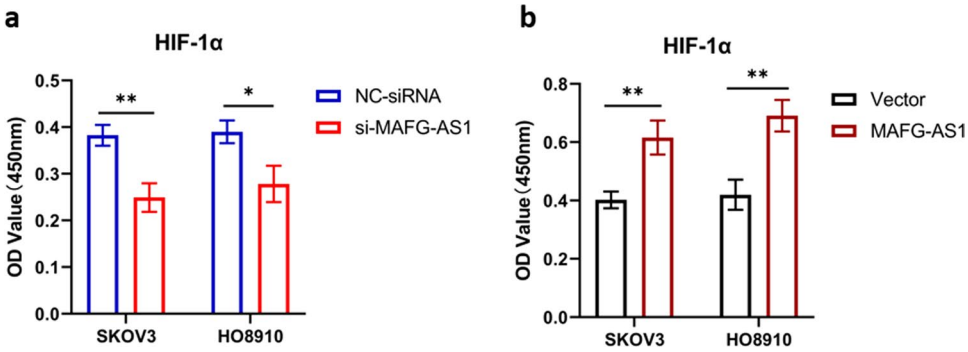

Fig. 6 The HIF-1α levels during (**a**) knockdown MAFG-AS1 and (**b**) overexpression MAFG-AS1

4 Discussion

Ovarian cancer is characterized by difficult early detection and easily recurrence [29]. Many studies have shown that MAFG-AS1 is highly expressed in various tumors [30–32]. In the previous study, it was demonstrated that MAFG-AS1 was abnormally strongly expressed, which was found that inhibition of MAFG-AS1 expression inhibited the proliferation, invasion, and metastasis of OC [33]. SKOV3 and HO8910 cells are commonly selected to explore the effects of target genes on OC cell proliferation, apoptosis, migration, invasion, and glycolysis. Firstly, we verified effects of MAFG-AS1 on ovarian carcinogenesis and development. We found that inhibition of MAFG-AS1 reduced OC cell proliferation, enhanced the amount of cells in G2 phase, and promoted apoptosis. Silencing MAFG-AS1 inhibit the glycolysi and affects HIF-1α in OC cells.

Metabolism is present in all living cells and includes the basic metabolism required to maintain basic cellular functions, cell division and proliferation, migration, and tissue-specific functions. Additionally, the metabolic activity in proliferating cells differs from that in non-proliferating cells. Glycolysis and oxidative phosphorylation are widespread in tumor cells and provide energy to tumor cells, but the production of ATP is more efficient during glycolysis compared to oxidative phosphorylation [34–36]. Thus, the "Warburg effect" present in tumor cells is necessary for the energy and biosynthesis required for rapid tumor cell proliferation. However, the role of oxidative phosphorylation in tumors cannot be completely ignored. Oxidative phosphorylation not only provides the cell with ATP, but also produces ROS, which are often accompanied by an acute inflammatory response, and in excess can lead to DNA damage and apoptosis [37]. Given that metabolic changes are closely linked to tumor proliferation, and our previous results suggest that downregulation of MAFG-AS1 can affect proliferation and apoptosis in OC, we speculate that this inhibitory effect may be mediated by altering the OC reprogramming of glycolytic metabolism. Presently, we observed association of MAFG-AS1 expression with cellular metabolism and affected the expression of the glycolytic regulator HIF-1α. Subsequently, silencing MAFG-AS1 expression in OC cells resulted in an inhibition of glucose uptakes and

lactate productions, and an increase in NAD^+/NADH ratio and ATP content. We also examined the levels of glycolysis and mitochondrial oxidative phosphorylation using ECAR and OCR, respectively, from which we discovered that silencing MAFG-AS1 inhibited glycolysis and enhanced oxidative phosphorylation. It was proven earlier that PKM2 is a speed-limiting enzyme of glycolysis and was highly represented in OC [38]. PKM2 translocated to the nucleus and complexes with HIF-1α, functioning as a transcriptional co-activator and promotion of HIF-1α targeted gene transcriptions [39]. Subsequent studies revealed that silencing MAFG-AS1 expression inhibited HIF-1α and thus acted as a repressor of the glycolytic process; this result was partially reversed by overexpressed MAFG-AS1. These support our hypothesis that MAFG-AS1 expression levels can inhibit glycolysis and promote oxidative phosphorylation in OC.

Our findings revealed that silencing MAFG-AS1 significantly reduced ATP levels, elevated the NAD^+/NADH ratio and enhanced oxidative phosphorylation. The silencing of MAFG-AS1 inhibited glycolysis, thereby reducing the supply of nucleotides and lipid precursors for macromolecular synthesis by tumor cells and inhibiting tumor growth. This also confirmed our previous speculation that MAFG-AS1 regulates the proliferation by affecting its metabolic reprogramming. Combined with the online database results, we found a direct positive correlation between MAFG-AS1 and HIF-1α, while HIF-1α glycolysis was crucial. Therefore, we speculate that MAFG-AS1 may affect the glycolytic reprogramming and proliferation through HIF-1α. Consistently, a previous study has demonstrated that lncRNA FAM83A-AS1 binds to HIF-1α at its N-terminal recognition site, thereby inhibiting HIF-1α degradation in OC cells [10]. Whereas, the regulatory mechanism of MAFG-AS1 on HIF-1α has not been explored, which is the limitation of this study and needs further investigation.

There are some limitations in our study. We only investigated the relationship between glycolysis-related gene HIF-1α and MAFG-AS1 in OC database, and did not identify the regulatory effect of glucose metabolism on cellular death. Further studies simultaneously performed MAFA-AS1 silencing and intervention with glucose metabolism key molecules (e.g., HK2, PFK1, GLUT1) will be useful to observe if metabolic changes affects cellular death in OC cells. Additionally, if MAFA-AS1 can interact with key metabolic regulators (e.g., AMPK, mTOR, HIF1α) or binds to the promoter region of glycolytic enzyme gene, this would strongly suggest a direct role of MAFA-AS1 in modulating glucose metabolism.

In summary, our study revealed that silencing MAFG-AS1 could inhibit the proliferation and induce apoptosis of OC cells by inhibiting the HIF-1α-mediated glycolysis process. Therefore, this study further revealed the potential mechanism of MAFG-AS1 in regulating OC cancerous behaviors, which is expected to provide a theoretical basis for the study of new targets for OC.

Acknowledgments None

Author contributions Liu Jia and Fei Yu wrote the main manuscript text prepared figures and did data analysis. All authors reviewed the manuscript."

Funding None.

Data availability The data that support the findings of this study are available from the authors but restrictions are, however, available from the authors upon reasonable request.

Declarations

Ethics approval and consent to participate All experimental procedures were conducted in strict accordance with the ethical standards of the Institutional Review Board of The Second Affiliated Hospital, Zhejiang University School of Medicine, and in compliance with the 1964 Declaration of Helsinki and its later amendments. Prior to initiation, the hospital's ethics committee approved the study. All methods were carried out per relevant guidelines and regulations. The authors affirm that no animals or humans were used in this study.

Consent for Publication Not applicable.

Competing Interests The authors declare no competing interests.

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