Dexmedetomidine Regulates Proliferation, Apoptosis, Migration, and Invasion in Ovarian Cancer Cells via MiR-155-HIF-1α Axis

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Background: Dexmedetomidine (DMED) is widely used as an adjuvant anesthetic, but how DMED regulates biological behavior of OC cells remains an area of active research. This study investigated the mechanism by which DMED regulates the proliferation, apoptosis, migration, and invasion abilities of OC cells.

Material/Methods: We determined the optimal concentration of DMED for use in treating SKOV3 cells. The biological activities of DMED-treated SKOV3 cells following transfection with miR-155 inhibitor or si-HIF-1α were measured by CCK-8 assay, flow cytometry, wound healing assay, and Transwell assay. qRT-PCR and Western blot analysis were performed to assess the expression levels of apoptotic-related caspase-3 and Mcl-1. Luciferase reporter assay verified the targeting relationship of miR-155 and HIF-1α.

Result: miR-155 was downregulated while HIF-1α was upregulated in SKOV3 cells. DMED dose-dependently reduced HIF-1α expression in SKOV3 cells, and upregulated the expression of miR-155. DMED inhibited the proliferation, migration and invasion abilities of OC cells, but also contributed to apoptosis of SKOV3 cells, while transfection of miR-155 inhibitor inhibited the effect of DMED on SKOV3 cells. In contrast, transfection with si-HIF-1α enhanced the effects of DMED on SKOV3 cells. HIF-1α was found to be a target gene of miR-155.

Conclusions: Our results suggest that DMED blocks cell proliferation, migration, and invasion and accelerates cell apoptosis in OC.

MeSH Keywords: Apoptosis • Cell Migration Assays • Cell Proliferation • Dexmedetomidine • Ovarian Neoplasms

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Background

Ovarian cancer (OC), which is the third most common cause of gynecologic malignancies, has the highest mortality rate among gynecologic malignancies [1,2]. The absence of distinctive symptoms and lack of effective and available screening approaches in clinical practice makes early diagnosis of OC difficult. Unfortunately, stage of diagnosis is a major factor that determines the survival rate of OC patients, and the average 5-year survival rate for OC patients is only 44% [3,4]. Although chemotherapy in advanced OC can achieve similar therapeutic efficiency as surgery, radical resection remains the primary treatment approach for OC [5,6]. Noticeably, anesthetic drugs must be properly used during OC surgery to avoid adverse effects of anesthesia, such as respiratory depression and unstable vital signs [7]. Therefore, selection of anesthetic drugs essential for OC radical surgery.

Dexmedetomidine (DMED) is a selective α₂-adrenoreceptor agonist that is a novel adjuvant analgesic-sparing agent used for reducing stress and protecting the cardiovascular system [8]. DMED can lead to local vasoconstriction, thus decreasing the systemic absorption and contributing to the safety and efficacy of intraperitoneal administration of local anesthetics [9]. Following cesarean section births, use of DMED can increase the analgesia effect from local anesthetics and can decrease adverse reactions [10]. In an OC rat model, DMED was found to inhibit activation of chemotherapy resistance pathways, thus improving therapeutic efficiency in patients with OC [11].

MicroRNAs (miRNAs) are mainly responsible for mediating the expression levels of many coding genes, consequently altering cellular pathways and thus affecting cell progression [12]. miR-155 can mediate DNA repair ability and sensitivity to ionizing radiation (IR) in triple-negative breast cancer [13]. Data also demonstrated that miR-155 can regulate cisplatin-induced apoptosis in OC by targeting X-linked inhibitor of apoptosis protein (XIAP), suggesting the protective role of miR-155 in OC progression by promoting cell apoptosis [14]. However, whether miR-155 can regulate cell activity in DMED-treated OC cells remains to be determined. In this report, we tested the hypothesis that HIF-1α is a target gene of miR-155. The miR-155-HIF-1α axis is a target gene of miR-155. The miR-155-HIF-1α-HO-1 signaling pathway was reported to be involved in DMED-regulated endotoxin-induced acute lung injury [15]. However, whether DMED can regulate the miR-155-HIF-1α-HO-1 signal pathway to affect the viability of OC cells remains an area of clinical uncertainty. In this regard, we hypothesize that DMED can regulate OC cell progression by the miR-155-HIF-1α axis. Therefore, this work was undertaken to analyze the mechanism by which DMED regulates the proliferation, apoptosis, migration, and invasion abilities of SKOV3 cells via the miR-155-HIF-1 axis.

Material and Methods

Cell culture

OC cells SKOV3 and ovarian epithelial cells HOSEpiC were purchased from American Type Culture Collection (ATCC, USA). Functionally, HOSEpiC cells were used as normal controls for OC cells. SKOV3 cells were cultured in RPMI-1640 culture medium ( GibCO, USA) containing 10% FBS and 1% double-antibody. The HOSEpiC cells were incubated in DMEM culture medium with 10% FBS and 1% double-antibody. The incubation of SKOV3 and HOSEpiC cells was performed at 37°C with 5% CO₂. DMED was purchased from Shanghai Lianshuo Biological Company. DMED of different concentrations (0, 1, 10, and 100 nM) were added to culture medium of SKOV3 cells. After 24-h incubation, culture medium was refreshed.

Cell transfection

SKOV3 cells were transfected with miR-155 inhibitor, miR-155 inhibitor negative control, si-HIF-1α, and its relative negative control (GenePharma, Shanghai). Lipofectamine 2000 transfection reagent (Invitrogen, USA) was used for transfection in accordance with its transfection instructions. Transfection experiments were conducted in triplicate.

qRT-PCR

Total RNAs were extracted using Trizol (Invitrogen, USA). The qualified RNAs were diluted to appropriate concentrations for reverse transcription using a reverse transcription kit (TakaRa, Japan). All operations were performed based on kit protocols. Real-time quantitative RT-PCR was performed with a LightCycler 480 (Roche, Switzerland) fluorescence quantitative PCR instrument. The reaction conditions were conducted using a fluorescent quantitative RT-PCR kit (SYBR Green PCR kit, Dongsheng Biology). The detailed conditions for PCR were as follows: pre-denaturation at 95°C for 5 min, denaturation at 95°C for 10 s, annealing at 60°C for 10 s, and extension at 72°C for 20 s, for a total of 40 cycles. Three replicates were set up. U6 was selected as the internal reference of miRNA, and GAPDH served as the internal reference of mRNA. The 2⁻ΔΔCT method was used to analyze data. The amplified primer sequences of each gene and its internal reference genes are detailed in Table 1.

Western blot analysis

Proteins were isolated and bathed in boiling water for 3 min for protein degeneration. The electrophoresis was conducted initially with 80 V for 30 min, and then 120 V for 1–2 h. The current of transfer membrane was 300 mA for 60 min. The current of transfer membrane was 300 mA for 60 min. After membrane transfer, the membrane was rinsed in washing solution for 1–2 min, and then sealed with blocking buffer.
at room temperature for 60 min, or incubated overnight at 4°C. Primary antibodies of rabbit anti-human GAPDH (S174T), HIF-1α (36169T), caspase-3 (9662S), Mcl-1(94296S), 1: 1000, Cell Signaling, Boston, USA) were added for incubation on a shaker at room temperature for 1 h. After that, the membrane was washed 3 times for 10 min each time. Then, the membrane was incubated with secondary antibodies (HRP-marked goat anti-rabbit IgG, 1: 5000, Beijing Kangwei Century Biology Co., Beijing, China) at room temperature for 1 h, followed by washing 3 times for 10 min each time. X-ray film was used for color pressing, developing, and fixing.

Luciferase reporter gene experiment

The online software TargetScan (http://www.targetscan.org/mamm_31/) was used to predict the binding sites of miR-155 and HIF-1α. According to the predicted results, wild and mutation sequences of binding sites were designed and synthesized, respectively (wt-HIF-1α and mut-HIF-1α). The wild sequence or mutation sequence on the binding site was inserted into the luciferase reporter gene vector (pGL3-Basic), and those 2 sequences were separately co-transfected with miR-155 mimic negative control (30 nM, GenePharma) into HEK239T cells (Shanghai Sixin Biological Co.). After transfection, firefly luciferase activity and Renilla luciferase activity were detected in each group. Renilla luciferase activity to Firefly luciferase activity was regarded as the ratio of luciferase activity. The experimental groups were named as follows: mimic NC+mut-HIF-1α group, mimic NC+wt-HIF-1α group, mimic+mut-HIF-1α group, and mimic+wt-HIF-1α group. Luciferase intensity was measured 3 times.

Table 1. Primer sequences used for RT-PCR.

| Name of primer | Sequences |
|----------------|-----------|
| miR-155-F      | GCAAGGTCGAGGATTTC |
| miR-155-R      | GTGGGATAGTGCTAAC |
| U6-F           | CTGCCTGGCGAGGACATATACT |
| U6-R           | AGCCTTCAAGATTTCCGTC |
| HIF-1α-F       | GTCTGTGACTACAAGCCC |
| HIF-1α-R       | TGGTAAAGAAATTACGGGGCA |
| Caspase-3-F    | GGGGATATCGCTGTCATGG |
| Caspase-3-R    | CCAGTACAGGAGCAGATGAC |
| Mcl-1-F        | GTTTTCAGCGACGGCG |
| Mcl-1-R        | AACGCCAACCTACCCG |
| GAPDH-F        | GTGGCCTGCTCAGAAAAGG |
| GAPDH-R        | GGGGATATCGCTGTCATGG |

F – forward; R – reverse; RT-PCR – reverse transcript polymerase chain reaction reaction.

CCK-8 assay

DMED-treated SKOV3 cells and suspensions of transfected SKOV3 cells of each group were seeded into 96-well plates (about 2000 cells in each well) with 3 replicates for per group. After incubation in an incubator for 24 h, 48 h, 72 h, and 96 h, 10 μl of CCK-8 solution (Mosak Biology) was added to each well. Then, after incubation for another 1–4 h, the absorbance at 450 nm wavelength was measured.

Flow cytometry

The density of DMED-treated SKOV3 cells and suspensions of transfected SKOV3 cells of each group were adjusted to 10⁴/ml. Then, 3 ml of cell suspension was collected from each group into a 10-ml centrifugal tube and centrifuged at 500 rpm for 5 min before the culture medium was discarded. The suspension was washed with PBS and centrifuged at 500 rpm for 5 min. Then, the supernatant was discarded. Cells were re-suspended in 100 μl of labeled solution and incubated for 10 min without light exposure. Annexin V-FITC (5 μl) and PI (5 μl) were added and gently mixed with cells for reaction for 10 min without light exposure. FITC fluorescence and PI fluorescence were measured using flow cytometry to analyze the apoptosis of SKOV3 cells. The migration ability of cells was measured 3 times.

Scratch test

DMED-treated SKOV3 cells and transfected SKOV3 cells in each group (2×10⁴ per well) after transfection were inoculated into 6-well plates. The cells in each group were inoculated into 3 wells and then incubated at 37°C with 5% CO₂ for 24 h until the cells formed a monolayer. Scratches were made on the monolayer cells with the tip of a pipette (sterile, 200 μl). Then, cells were washed with PBS before incubation at 37°C with 5% CO₂ for 24 h. Scratch widths were observed and recorded under a microscope (200×) after culturing for 0 h and 24 h. Migration rates of OC cells were analyzed based on scratch area. Migration rate=(0 h scratch distance–24 h scratch distance)/0 h scratch distance.

Transwell

Matrigel matrix gel (50 μg/ml) was mixed with serum-free RPMI-1640 medium at a ratio of 1: 5. Mixed matrix glue (80 μl) was laid in a Transwell chamber with an 8-μm aperture and placed on 24-well plates at 37°C for 6 h to solidify the gel. OC cells in each group were collected after treatment for 48 h. Serum-free RPMI-1640 medium was applied to adjust the cell concentration of each group to 2×10⁴/ml. We then added 200 μl of cell suspension to the upper chamber and we added 600 μl of RPMI-1640 medium with 1% low-serum to the lower chamber.
After 24 h of incubation at 37°C and 5% CO₂, the chamber was taken out. After PBS washing, methanol fixation and crystal violet staining, 5 visual fields were randomly selected under an inverted microscope to count cells. The number of cells passing through the Matrigel matrix gel was used to express the invasive ability of cells. Three multiple wells were set up in each experiment.

Statistical analysis

GraphPad software (version 7.0) was used for statistical analysis. All data are expressed as the mean value and standard deviation (±s). We used the t test to compare differences between 2 groups. One-way analysis of variance was used for comparison among groups. Dunnett’s multiple comparisons test was performed for the post hoc comparison/test. P<0.05 was regarded as having statistical significance.

Results

Decreased miR-155 and increased HIF-1α in OC cells

The expression levels of miR-155 and HIF-1α in OC cells and HOSEpiC cells were measured by qRT-PCR and Western blot analysis, showing that miR-155 in SKOV3 cells was clearly lower than in HOSEpiC cells (Figure 1A), but the mRNA and protein expression levels of HIF-1α in SKOV3 cell were obviously higher than in HOSEpiC cells (Figure 1B, 1C).

DMED regulates miR-155 and HIF-1α levels in OC cells

SKOV3 cells subjected to DMED treatment (with concentrations of 0, 1, 10, and 100 nM) had elevated expression of miR-155 (Figure 2A) and decreased expression of HIF-1α, and these differences were dose-dependent (Figure 2B, 2C). SKOV3 cells treated with 10 nM of DMED had substantially upregulated miR-155 and notably downregulated expression of HIF-1α. Therefore, 10 nM of DMED was selected for the following assays to explore the effects of DMED on OC biological behavior.

DMED upregulates miR-155 to mediate proliferation, apoptosis, migration, and invasion of OC cells

Transfection with miR-155 inhibitor reduced miR-155 expression in SKOV3 cells, but its expression was upregulated after DMED treatment. SKOV3 cells subjected to miR-155 inhibitor transfection and DMED treatment had substantially decreased miR-155 expression compared with cells treated with DMED alone (Figure 3A). After transfection of miR-155 inhibitor, the proliferation (Figure 3B), migration (Figure 3F), and invasion abilities (Figure 3G) of SKOV3 cells were enhanced, while...
cell apoptosis (Figure 3C) was clearly suppressed, as evidenced by increased expression level of Mcl-1 and decreased expression level of caspase-3 (Figure 3D, 3E). However, the expression profile in DMED-treated SKOV3 cells was the opposite of cells transfected with miR-155 inhibitor. In cells subjected to DMED treatment and miR-155 inhibitor transfection, the effect of DMED on the proliferation, apoptosis, migration, and invasion of SKOV3 cells was offset by transfection of miR-155 inhibitor. These results demonstrate that DMED regulates OC cell progression by upregulating miR-155 expression.

HIF-1α is a target gene of miR-155

After transfection with si-HIF-1α, the expression of HIF-1α in SKOV3 cells was significantly decreased, while in SKOV3 cells transfected with miR-155 inhibitor, the expression of HIF-1α was notably increased (P<0.05) (Figure 4A, 4B). The binding site between miR-155 and HIF-1α is represented in Figure 4C. There was no difference of luciferase activity between the mimic NC+mut-HIF-1α group and mimic+mut-HIF-1α group, whereas luciferase activity in the mimic+wt-HIF-1α group was significantly reduced (mimic+wt-HIF-1α group vs. mimic NC+wt-HIF-1α group) (Figure 4D), suggesting that miR-155 can bind with HIF-1α.

DMED regulates proliferation, apoptosis, migration, and invasion of OC cells via miR-155-HIF-1α axis

Transfection of si-HIF-1α in DMED-treated SKOV3 cells can inhibit cell proliferation (Figure 5A), migration (Figure 5E), and invasion (Figure 5F), and enhance cell apoptosis (Figure 5B), as shown by increased level of caspase-3 expression and under-expression of Mcl-1 (Figure 5C, 5D). These results suggest that HIF-1 deficiency further enhances the inhibitory effect of DMED on OC cells; therefore, DMED may inhibit OC progression through reducing HIF-1α expression. The biological activity of DMED-treated SKOV3 cells co-transfected with si-HIF-1α and miR-155 inhibitor showed a different expression pattern from that in DMED-treated SKOV3 cells transfected with si-HIF-1α, which suggests that miR-155 affects the biological behavior of OC cells via controlling and targeting HIF-1α, while DMED inhibits OC development via the miR-155-HIF-1 axis.

Discussion

To investigate the mechanism of DMED in the development of SKOV3 cells, the expression levels of miR-155 and HIF-1α in ovarian epithelial cells HOSEpiC and DMED-treated OC cells were first examined. Then, we knocked down miR-155 and
HIF-1α expression levels to observe how miR-155 and HIF-1α suppression can regulate OC cell activity. Dual-luciferase reporter assay further identified the binding of miR-155 and HIF-1α. The results from this study support that DMED can inhibit the progression of OC cells by regulating the miR-155-HIF-1 axis.

Although genetic factors and environmental factors are well-known risk factors for OC [1], the detailed biological mechanism of OC occurrence still remains unknown. The biological function of OC cells can be regulated by many miRNAs whose downregulation or overexpression has been detected in OC cells [16,17]. The first major finding in this study illustrated
that miR-155 expression in SKOV3 cells was notably decreased, whereas the expression of HIF-1α behaved in the opposite fashion when compared with that in HOSEpiC cells. We speculate that the dysregulation of miR-155 and HIF-1α might be involved in OC development. Further, the expression of miR-155 in DMED-treated cells was detected, supporting the regulatory role of DMED in miR-155 expression. Inflammation after surgery can promote cancer progression and metastasis, and DMED can decrease the risk of surgery-related tumor metastasis through inhibiting inflammation and exerting a sedative function [18]. In addition, administration of DMED can provide clinical benefits in oxygenation and lung mechanics for patients complicated with lung cancer and chronic obstructive pulmonary disease [19], but whether DMED provides similar benefit for OC patients remains to be explored. This study also clarified that HIF-1α is a target gene of miR-155. This result is in agreement with the conclusion in a prior study that found certain miRNAs, such as miR-155, can control HIF-1α so as to form the HIF-1α-miR-155 pathway to maintain oxygen homeostasis [25]. Knockdown of HIF-1α enhances cisplatin resistance in OC cells, and the pathway underlying HIF-1α-adjusted tumor metabolism could be a new target for miR-155 plays an important role as a tumor suppressor miR. Elevated serum expression of miR-155 was detected in osteosarcoma, and miR-155 has the potential to predict relapse of breast cancer [20,21]. Furthermore, accumulating evidence has emerged regarding the dysregulation of miR-155 in development of breast cancer drug resistance [22]. Consistent with our study, miR-155 was reported to regulate cell growth and proliferation of melanoma cells and to serve as a tumor suppressor [23]. Furthermore, miR-155 was long ago found to be down-regulated in OC cells and had antiproliferative and pro-apoptotic activity in OC by targeting claudin-1 [24]. However, the role of miR-155 in DMED-treated OC cells has been unclear.

**Figure 4.** HIF-1α was a target gene of miR-155. The expression of HIF-1α in SKOV3 cells was measured by (A) qRT-PCR and (B) Western blot; (C) The binding site between miR-155 and HIF-1α was on the 3'UTR; (D) The binding of miR-155 with HIF-1α was verified by luciferase reporter gene assay; * P<0.05, ** P<0.01, compared inhibitor NC group or mimic NC+wt-HIF-1α group; NC – negative control.

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Figure 5. DMED regulates miR-155-HIF-1α axis to mediate cell proliferation, apoptosis, migration, and invasion of OC cells. (A) Cell proliferation was inspected by CCK-8 assay; (B) Cell apoptosis was determined with flow cytometry; (C, D) The mRNA and protein expression levels of caspase-3 and Mcl-1 were separately detected by qRT-PCR and Western blot; (E) Cell migration was detected by wound healing assay; (F) Cell invasion was determined using Transwell assay; * P<0.05, ** P<0.01, compared to DMED group; # P<0.05, ## P<0.01, compared to DMED+si-HIF-1α group; DMED – dexmedetomidine.
overcoming cisplatin resistance in OC [26]. Our study further offers important evidence supporting our hypothesis that HIF-1α is involved in OC. Therefore, we assessed the miR-155-HIF-1α pathway in therapy of OC. In the present work, transfection with miR-155 inhibitor inhibited the effects of DMED on the development of SKOV3 cells, while transfection with si-HIF-1α promoted the effects of DMED on proliferation, apoptosis, migration, and invasion abilities of SKOV3 cells. These experiments further verified that DMED directly regulates miR-155 and HIF-1α expression levels. It has become increasingly clear that DMED affects the progression of OC via the miR-155-HIF-1α pathway.

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Conclusions

Taken together, our research provides ample evidence that DMED affects the development of OC cells via the miR-155-HIF-1α pathway. Our results show the distinctive role of DMED in controlling OC progression and may have the possibility to be widely used for OC patients, possibly providing a new approach to treatment of OC. Considering the complicated biological mechanism and varied functions of DMED, further studies are required to better elucidate the roles of DMED in the biological behavior of OC cells.

Conflict of interests

None.