THE EFFECT OF DEXMEDETOMIDINE ON BREAST CANCER CELL GROWTH AND METASTASIS BY REGULATING THE EXPRESSION OF CIRCRNA AND ITS EFFECT MECHANISM

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ABSTRACT

Objective: *The present study aims to study the effect of dexmedetomidine on the growth and metastasis of breast cancer cells by regulating the expression of circular RNA (circRNA) and its mechanism.*

Methods: *As many as 25 pairs of freshly frozen breast cancer tissues and adjacent normal tissues were collected from the Second Municipal Affiliated Hospital. Breast adenocarcinoma cells MDA-MB-231 were purchased from the American Type Culture Collection. According to the purpose of the experiment, the obtained tissue samples were divided into healthy control group (normal tissue) and observation group (breast cancer tissue). According to cultured cells, they were divided into: MDA-MB-231 group (cells cultured under normal conditions) and dexmedetomidine treatment group (1μM dexmedetomidine cultured cells). The researchers obtained the informed consent from each patient, and the study was approved by the ethics committee of the First Hospital. The expression of circRNA in the tissue samples and cell lines of the different treatment groups was analyzed by RT-PCR. The cell proliferation of the two groups was determined by MTT following 24h, 48h and 72h. Transwell migration was carried out to detect cell invasion and migration. CCK-8 was used to detect cell viability. The protein expression of α2-ADR and STAT3 in the cells was analyzed by Western blot.*

Results: *The mRNA expression of circPGAP3, circANKS1B and circTHSD4 in the observation group was higher than that of the healthy group (P<0.05), and the mRNA expression of circ CYP24A1 in the observation group was lower than that in the healthy group (P<0.05). The mRNA expression of circPGAP3, circANKS1B and circTHSD4 in the dexmedetomidine group was higher than that of the MDA-MB-231 group (P<0.05), and the mRNA expression of circ CYP24A1 in the dexmedetomidine group was lower than that of the MDA-MB-231 group (P<0.05). The absorbance value of the dexmedetomidine treatment group was higher than that of the MDA-MB-231 group following 24h and 48h (P<0.05), and the absorbance value of the dexmedetomidine treatment group was higher than that of the MDA-MB-231 group following 72h (P<0.05). The number of cell invasion and cell migration in the dexmedetomidine treatment group was higher than that of the MDA-MB-231 group (P<0.05). The apoptosis rate of the dexmedetomidine treatment group was lower than that of the MDA-MB-231 group (P<0.05), and the cell viability of the dexmedetomidine treatment group was higher than that of the MDA-MB-231 group (P<0.05). The protein expression of α2-ADR and STAT3 in the dexmedetomidine treatment group was higher than that of the MDA-MB-231 group (P<0.05).*

Conclusion: *dexmedetomidine promoted the growth and migration of breast cancer cells by regulating the expression of circRNA.*

Keywords: *Dexmedetomidine, breast cancer, cell proliferation, migration and invasion, apoptosis.*

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Introduction

Breast cancer is one of the most common cancers affecting women all over the world. Because of the high recurrence rate and metastasis rate, the prognosis is poor for breast cancer patients[1]. Breast cancer can be divided into four main molecular subtypes. Metastasis accounts for more than 90% of mortality in breast cancer patients. Due to the spatio-temporal intratumor heterogeneity during metastasis, there is still a lack of effective therapeutic agents targeting metastasis[2]. Therefore, it is urgent to clarify the potential mechanism of metastasis to provide novel treatment strategies for patients with metastasis breast cancer. Dexmedetomidine is a new generation of α2-adrenergic receptor agonist with high selectivity, it can be used as an adjuvant of sedatives and anesthetics during the

perioperative period[3]. Dexmedetomidine increases retention and metastasis of tumor cells in rat breast adenocarcinoma mainly through α2-adrenergic receptor[4]. A prospective randomized clinical study using breast cancer cell line MCF-7 shows that patients who had received 2μg/kg dexmedetomidine for 2h during operation had higher proliferation, migration, and invasion than those who had not received a normal saline[5]. Perioperative use of dexmedetomidine may have harmful effects on the prognosis of breast cancer.

However, the potential mechanism of dexmedetomidine in promoting breast cancer cell migration is still elusive. Dexmedetomidine plays an important role in various biological processes by binding to α2-adrenergic receptors[6]. Dexmedetomidine may increase the proliferation, migration and invasion of breast cancer cells by regulating the α2-adrenergic receptor/Erk1/2 signaling pathway[7]. In recent years, the role of circRNA in cancer has attracted a great deal of attention. CircRNA is highly conservative and stable, characterized by no covalent closed-loop structure of 5'-cup structure and 3'-polyadenylic acid tail. With the appearance of high-throughput sequencing, it is now known that circRNA is not only a by-product of splicing errors, but also a product of new regulating alternative splicing[8,9].

CircRNA is a cis-element and trans-acting factor formed by reverse splicing of exons or introns with gene regulation ability. circRNA participates in a variety of cancer biological processes, including EMT and metabolism, by interacting with MicroRNA (MicroRNA)[10]. Although a lot of progress has been made in investigating circRNA, the potential correlation between circRNA and breast cancer metastasis has not yet been elucidated. In this study, breast cancer cells treated with dexmedetomidine could be used to study the mechanism of circRNA expression and tumor characteristics.

Materials and methods

Tissue samples

Twenty-five pairs of fresh frozen breast cancer tissues and adjacent normal tissues (observation group and healthy control group) were collected, excluding patients who received any anti-tumor treatment before operation.

Pathological sections were independently identified by two pathologists. Among them, all tissue sections were verified by circRNA. The experiment obtained the informed consent of each patient, and the research was approved by the hospital's ethics committee.

Cell culture and treatment

Human breast adenocarcinoma Cell MDA-MB-231 was purchased from American Type Culture Collection (ATCC, USA). MDA-MB-231 cells were cultured in Dulbecco modified Eagle medium in a humid environment with a humidity of 5% and a temperature of 37°C after being supplemented with 10% fetal bovine serum (Gibco/Thermo company, USA) and 1% penicillin-streptomycin (Fisher Scientific, USA), and they were then treated with 1μM dexmedetomidine (following 24h, 48h and 72h).

Experimental grouping

According to the experimental purpose, the obtained tissue samples were divided into healthy control group and observation group. According to the cultured cells, they were divided into MDA-MB-231 group (cells cultured under normal conditions) and dexmedetomidine treatment group (dexmedetomidine cultured cells with 1μM concentration).

Reverse transcription and real-time polymerase chain reaction (RT-qPCR)

Total RNA was separated from tissue samples, and cells were cultured with TRIzol reagent (Invitrogen Company, USA). The amount of RNA was measured by SmartSpec Plus spectrophotometer (Bio-Rad). According to the manufacturer's instructions, 2μg RNA was reversely converted into complementary DNA(cDNA) using SuperScript™ III first-strand synthesis kit (Invitrogen Company, USA). PCR reaction included 1×SYBR Green PCR Master Mix (Biorad Company, USA), 2μL cDNA and 0.2μM specific primer pair. Real-time PCR was carried out on 7500 fast real-time PCR system by two-step PCR program: 1 cycle for 10min at 95°C; 40 cycles at a speed of 15 seconds a cycle at 95°C, 45 seconds a cycle at 56°C and 30 seconds a cycle at 72°C. The relative expression level of TMPRSS2 was calculated by $2^{-\Delta\Delta Ct}$ method normalized to the housekeeping gene GAPDH. The multiple changes of control were presented and compared.

Western blot analysis

MDA-MB-231 cells were harvested and lysed in lysis buffer (Vazyme Company, Nanjing) containing 1mM PMSF and complete protease

inhibitor mixture (Roche, Germany). The cell lysate was kept on ice for 30min and centrifuged at 12,000g for 10min. The BCA protein detection kit (Vazyme Company, Nanjing) was used to analyze the protein concentration. Protein samples were collected and separated on 10% sodium dodecyl sulfate (SDS)-polyacrylamide gel and transferred to polyvinylidene fluoride (PVDF) membrane.

The membrane was sealed with 5% skimmed milk at 37°C for 2h, and cultured with anti-human GAPDH primary antibody, α2B-adrenergic receptor and STAT3 antibody (diluted at 1:1000 at 4°C; Santa Cruz Biotechnology Company, USA). After being washed with TBST 3 times, the membrane was incubated with HRP conjugated secondary antibody (diluted at 1: 2000; Santa Cruz Biotechnology Company, USA) at room temperature for 1h. Chemiluminescence reagent (Millipore Company, USA) was used to detect the immunoreaction band, and measurement was carried out by a densitometer.

Cell proliferation assay

The assay of 3-(4,5- dimethyl-2-thiazolyl) -2 and 5-diphenyltetrazolium bromide (MTT) (Promega Company, USA) was performed according to the manufacturer's instructions so that the proliferation of MDA-MB-231 cells would be analyzed.

Cells (2000 cells/well) were inoculated on a 96-well microtiter plate and incubated overnight to create cell adherence. Cells were treated with different concentrations of dexmedetomidine and incubated for 48h. MTT solution was added to each well. The cells were incubated at 37°C for 4h. The absorbance was measured at 570nm using a microplate reader (Molecular Devices Company, USA).

Cell viability assay

According to the manufacturer's instructions, cell viability was determined by cell counting kit (CCK-8) assay (KeyGEN BioTECH). The RA-FLSs was implanted into a 96-well plate with a density of 2.0×10^3/ well, and cultured in 100μLLDMEM medium containing 10%(v/v) FBS. The absorbance was measured at 450nm with a microplate reader.

Transwell analysis

The invasion of MDA-MB-231 cells was evaluated by Transwell filter (well size of 8m, Beary Card Company, USA). A total of $1x10^5$ cells treated with dexmedetomidine were re-suspended in 400μL serum-free medium and inoculated into the filter coated with Matrigel in the upper chamber. 600μL L15 medium containing 20% FBS was added to the lower chamber as a chemotactic agent. After 48h, the non-invasive cells in the upper chamber were removed by cotton swabs.

Infiltrated cells in the lower chamber were fixed by 4% paraformaldehyde and stained with 1% purple crystals. The number of invading cells was imaged using an inverted microscope (Olympus Corporation, Japan) and counted in five randomly selected fields.

Statistical analysis

This study was analyzed by SPSS20.0 (IBM Company, USA); the measurement data was expressed by "mean ± standard deviation" ($\bar{x}\pm s$), and the comparison between groups is made by independent sample t-test; the counting data was expressed by percentage (%), and the comparison between groups was analyzed by χ^2; the significance level ($P<0.05$) indicated a statistically significant difference.

Results

Regulation of expression of circRNA in tissues by dexmedetomidine

RT-qPCR analysis showed that the mRNA expression of circPGAP3, circANKS1B and circTHSD4 in the observation group was higher than that of the healthy group ($P<0.05$), while the mRNA expression of circCYP24A1 in observation group was lower than that of the healthy group ($P<0.05$). (Table 1).

Group	circPGAP3	circANKS1B	circTHSD4	circCYP24A1
Healthy control group (n=25)	1.15±0.12	1.08±0.09	1.04±0.10	2.37±0.38
Observation group (n=25)	2.08±0.29	2.34±0.34	1.97±0.20	1.15±0.12
t value	5.038	4.127	6.821	5.688
P value	0.026	0.013	0.005	0.017

Table 1: RT-qPCR analysis of expression of circRNA related genes in tissues ($\bar{x}\pm s$).

Regulation of expression of circRNA in cell line by dexmedetomidine

The expression of circRNA in cell lines of different treatment groups was analyzed by RT-PCR. Compared to MDA-MB-231 group, the mRNA expression of circPGAP3, circANKS1B and circTHSD4 in dexmedetomidine group increased ($P<0.05$), while the mRNA expression of circCYP24A1 in dexmedetomidine group decreased ($P<0.05$). (Figure 1, Table 2).

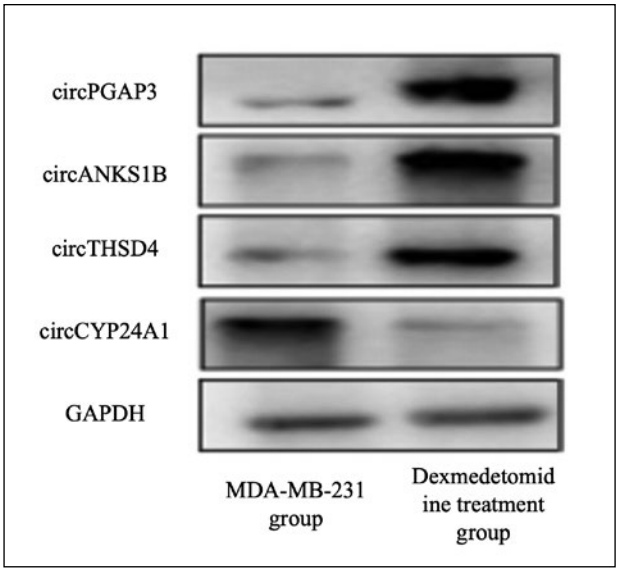

Figure 1: RT-qPCR analysis of expression of circRNA related genes in cell lines.

Group	circPGAP3	circANKS1B	circTHSD4	circCYP24A1
MDA-MB-231 group (n=25)	1.28±0.15	1.17±0.14	1.23±0.16	2.18±0.23
Dexmedetomidine treatment group (n=25)	2.74±0.31	3.05±0.45	2.68±0.27	1.02±0.10
t value	5.039	4.127	6.518	5.288
P value	0.023	0.034	0.011	0.027

Table 2: RT-qPCR analysis of expression of circRNA related genes in cell lines ($\bar{x}\pm s$).

Assay of cell proliferation by MTT

The cell proliferation of the two groups was measured by the MTT method following 24h, 48h, and 72h. The absorbance of dexmedetomidine treatment group at 24h and 48h was higher than that of MDA-MB-231 group (P<0.05), and the absorbance of dexmedetomidine treatment group following 72h was higher than that of MDA-MB-231 group (P<0.05); this indicates that dexmedetomidine promoted the proliferation of breast cancer cells. (Table 3).

Group	24h	48h	72h	F value	P-value
MDA-MB-231 group (n=25)	2.16±0.23	3.44±0.41	4.53±0.62	15.859	0.001
Dexmedetomidine treatment group (n=25)	4.37±0.25	7.51±0.67	11.33±1.28	19.527	0.001
t value	5.017	4.552	6.178	-	-
P value	0.026	0.031	0.001	-	-

Table 3: Assay of cell proliferation by MTT ($\bar{x}\pm s$).

Assay of cell migration and invasion

Compared with MDA-MB-231 group, the migration and invasion capacity of cells in the dexmedetomidine treatment group increased (P<0.05), and dexmedetomidine promoted the migration and invasion of breast cancer cells. (Figure 2, Table 4).

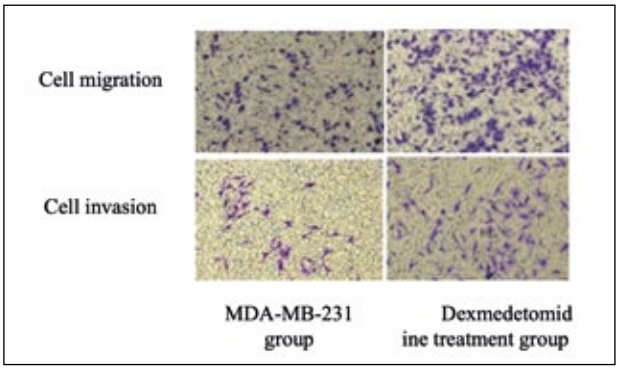

Figure 2: Comparison of assay of cell migration and invasion.

Group	Cell invasion	Cell migration	*F* value	*P*-value
MDA-MB-231 group (n=25)	116.28±8.54	129.83±12.67	12.995	0.001
Dexmedetomidine treatment group (n=25)	195.35±13.52	225.37±19.54	25.365	0.001
t value	6.339	5.218	-	-
P value	0.022	0.037	-	-

Table 4: Assay of cell migration and invasion ($\bar{x}\pm s$).

Assay of cell viability and apoptosis

The cell viability was detected by CCK-8. Compared to MDA-MB-231 group, the apoptosis rate of dexmedetomidine treatment group decreased (P<0.05), while the cell viability of dexmedetomidine treatment group increased (P<0.05). (Table 5).

Group	Cell apoptosis (%)	Cell viability (%)	*F* value	*P*-value
MDA-MB-231 group (n=25)	116.28±8.54	129.83±12.67	12.995	0.001
Dexmedetomidine treatment group (n=25)	195.35±13.52	225.37±19.54	25.365	0.001
t value	6.339	5.218	-	-
P value	0.022	0.037	-	-

Table 5: Cell viability and apoptosis ($\bar{x}\pm s$).

Western blot analysis of α2-adrenoceptor/ STAT3 signal

The expression of α2-ADR and STAT3 protein in cells was analyzed by western blot. The expression of α2-ADR and STAT3 protein in dexmedetomidine treatment group was higher than

that of MDA-MB-231 group (P<0.05); this indicates that dexmedetomidine could activate α2-adrenergic receptor/STAT3 signaling pathway. (Table 6).

Group	α2-AdR	STAT3	*F* value	*P*-value
MDA-MB-231 group (n=25)	1.36±0.14	1.13±0.11	16.257	0.001
Dexmedetomidine treatment group (n=25)	2.37±0.42	1.97±0.23	19.663	0.001
t value	5.068	4.127	-	-
P value	0.015	0.033	-	-

Table 6: Western blot analysis of α2-ADR and STAT3 expression ($\bar{x}\pm s$).

Discussion

Breast cancer is one of the most common and invasive tumors, and it is the leading cause of cancer death in females in the world. Although plenty of progress has been made in early detection and diagnosis, the incidence of breast cancer patients is still rising after undergoing surgery and radiotherapy or chemotherapy[11]. Accumulated evidence shows that the poor prognosis of breast cancer patients is mainly due to the high recurrence and metastasis of breast cancer cells[12]. Therefore, understanding the mechanism related to the progression and development of these cells is of great significance to improve the survival rate of breast cancer patients. Adrenaline receptor is a member of G protein-coupled receptors and plays a key role in various biological processes by binding with catecholamine[13]. It has been proved that α2-adrenergic receptor is expressed in human breast cancer cell lines, and tramadol can inhibit the proliferation, migration and invasion of human breast cancer cells through α2- adrenergic receptor signaling, suggesting that α2--adrenergic receptor may be a key regulatory factor in human breast cancer[14].

Dexmedetomidine is an agonist of α2-adrenoceptor, which is used as a sedative and an adjuvant in anesthesia strategy during the perioperative period. It is unique in its sedative, anti-anxiety, analgesic, and sympathetic functions, and shows sparse functions of opioids and anesthetics[15]. Given these effects of dexmedetomidine, especially its sympathetic nerve effect, beneficial behaviors can be assumed in perioperative nursing care of cancer patients. However, in vitro studies, it has been shown that dexmedetomidine can improve cell survival rate and cell proliferation[16]. Recent studies have shown that anesthetics such as morphine and propofol may affect malignant tumors of solid tumors. The function of dexmedetomidine in the tumorigenesis of breast cancer cells is still unknown. In this study, we found that dexmedetomidine could increase the proliferation, migration and invasion of MDA-MB-231 cells in a dose-dependent manner through activating α2- adrenoceptor /ERK signaling pathway. In addition, dexmedetomidine also promotes the growth of established tumors in vivo. Overall, these data indicate that dexmedetomidine may not be suitable for cancer surgery to avoid the risk of recurrence and metastasis after cancer surgery. In recent years, although early diagnosis and targeted therapy have greatly reduced the mortality of breast cancer patients, drug resistance to recurrence, metastasis, and radiotherapy and chemotherapy are still inevitable problems in clinical treatment of breast cancer. It has been found that breast cancer is the result of many genetic disorders, proving that the occurrence and development of breast cancer are influenced by the intracellular gene network system.

According to length and structure, non-coding RNA (ncRNA) can be divided into long non-coding RNA (lncRNA), miRNA and newly discovered circRNA. These ncRNA play a vital biological function in their sequence or structural characteristics[17]. Structurally, the length of miRNA is about 21-23 nucleotides. The LncRNA contains more than 200 nucleotides, some of which even exceed 100,000 nucleotides[18]. CircRNA, as a new type of ncRNA, has a polar structure and a cyclized structure of polyA tail. Functionally, miRNA regulates protein expression by directly inhibiting its target gene. It acts as a regulator and an inhibitor of DNA polymerase II during transcription, and can participate in mRNA processing and translation at the post-transcriptional level[19]. CircRNA is a new type of extensive and diverse endogenous non-coding RNA produced by non-standard reverse splicing events, playing a key role in many biological processes. CircRNA has been characterized in various cell lines and found to be involved in many biological processes related to the pathogenesis of many diseases, including diabetes and many vascular diseases. In addition, circRNA is reported to be involved in the neural regulation system. It is found that most circRNA is involved in protein or microRNA chelation, transcription regulation, splicing interference and translation to produce polypeptide at molecular level. On the contrary, there are few studies on circRNA at present. Unlike

ordinary RNA, circRNA has a closed-loop structure, and has high abundance in eukaryotic transcriptome. Most circRNA is transcribed from exons, and their sequences are highly conserved among different organisms. CircRNA has the characteristics of tissue specificity and expression specificity in different stages. In this study, we identified a large number of circRNA through RNA sequences. Some circRNA were identified. They are highly associated with invasion and metastasis of breast cancer as well as poor prognosis. Functionally, circRNA promotes invasion and metastasis of breast cancer cells without affecting proliferation and apoptosis. More and more evidence shows that circRNAs are abundant, stable and highly conserved among eukaryotes with gene regulation ability. Here, we also identified many circRNA, most of which were generated from precursor mRNA by exon cyclization. Up to now, many circRNAs have been identified as biomarkers for diagnosis and prognosis of human malignant tumors, such as colorectal cancer (CiRS-7 and circHIPK3), gastric cancer (circPVT1), hepatocellular carcinoma (circMTO1 and circSMARCA5) and bladder cancer (circMYLK and circITCH)[20].

Compared to traditional linear RNA, nucleases are more stable in cells because they cannot degrade circRNA. CircRNA, as a competitive endogenous RNA in cytoplasm, eliminates the suppressed target genes by sponging this miRNA. At present, some important circRNAs in breast cancer have been found, such as circPGAP3, circANKS1B, circTHSD4 and circCYP24A1. In this study, the expression of circRNA in 25 pairs of TNBC and adjacent normal tissues was analyzed by RT-qPCR. qRT-PCR analysis, showing that the mRNA expression of circPGAP3, circANKS1B and circTHSD4 in the observation group was higher than that of the healthy group. The expression of circCYP24A1mRNA in observation group was lower than that of the healthy group, indicating that these circRNAs were closely related to the occurrence of breast cancer. In addition, MDA-MB-231 was used to test the expression of these circRNAs, and it was found that dexmedetomidine treatment promoted or inhibited the expression of these circRNAs.

In the current study, the expression of α2-adrenergic receptor increased within 48h in MDA-MB-231 treated with 1μM dexmedetomidine. The expression of α2-ADR and STAT3 in cells was analyzed by western blot, indicating that dexmedetomidine could activate α2-adrenergic receptor /STAT3 signaling pathway. MDA-MB-231 cells were treated with dexmedetomidine, and the effect of dexmedetomidine on the proliferation of breast cancer cells was measured by an MTT assay. The absorbance of dexmedetomidine treatment group was higher than that of the MDA-MB-231 group following 24h, 48h and 72nd, indicating that dexmedetomidine promoted the proliferation of breast cancer cells. Transwell filter was used to evaluate the migration and invasion of MDA-MB-231 cells, and the cells treated with dexmedetomidine showed a higher migration quantity and a higher invasion ability. According to the detection of cell viability, the cell viability in dexmedetomidine treatment group was higher than that of the MDA-MB-231 group, indicating that dexmedetomidine inhibited the apoptosis of breast cancer cells.

To sum up, dexmedetomidine could promote the proliferation, migration and invasion of MDA-MB-231 cells by regulating circRNA/α2B-adrenoceptor/STAT3 signaling pathway, indicating that dexmedetomidine may not be suitable for the surgical treatment of breast cancer patients.

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