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Original Article

Arsenic Trioxide Affects the Proliferation of Gastric Cancer Cells through MiR-885-5p/CDC73 Axis

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Abstract

Background: To explore Arsenic trioxide (As_2O_3) and its regulated miR-885-5p/CDC73 signaling pathway involved in the development of gastric cancer.

Methods: Fifty-two healthy patients and patients with gastric cancer were enrolled 2019-2020 in He Xian Memorial Hospital, Guangzhou, China. The patients with gastric cancer were divided into control group and As_2O_3 administration group. After 2 courses of treatment, their peripheral blood was collected to analyze the therapeutic effect. miR-885-5p expression in peripheral blood was analyzed by qRT-PCR. As_2O_3 was added into MGC-803 gastric cancer cell line at 0, 10, 20, 40 and 80 μmol/L. The proliferation rate and 48h IC50 value of gastric cancer cells were investigated by CCK-8, and the effect of As2O3 on miR-885-5p expression in the cells was analyzed.

Results: After 4 weeks of treatment, the objective efficiency of control group and As_2O_3 administration group was 17.3% and 13.4%, respectively, without significant statistical difference. The overall benefit rate of As_2O_3 administration group was significantly higher than that of the normal treatment group (P=0.049). qRT-PCR experiment results found that miR-885-5p significantly highly expressed in peripheral blood in the As_2O_3 administration group, while miR-885-5p in gastric cancer was lower compared with normal people. Adding As_2O_3 to the gastric cancer cells could significantly inhibit miR-885-5p expression, while miR-885-5p in gastric cancer cells affected cell expression by targeted regulation, affecting cell proliferation.

Conclusion: As_2O_3 may be used as a drug treatment program for gastric cancer, and mainly regulates the proliferation of gastric cancer cells by affecting the miR-885-5p/CDC73 target axis to participate in the development of gastric cancer.

Keywords: Gastric cancer; Arsenic trioxide; Immunology; Cell proliferation

Introduction

In recent years, relevant statistics showed that the incidence and mortality of gastric cancer are increasing year by year. There were 951,000 cases of new gastric cancer worldwide in 2012 (1), with 723,000 deaths, and the patients' age is becoming increasingly younger. As the fifth most common

tumor in the world, gastric cancer have no obvious symptoms at early stage, only a few symptoms such as nausea, vomiting or upper gastrointestinal symptoms such as ulcers. Unlimited proliferation of the typical features of gastric cancer will lead to the continuous growth, invasion and metastasis of the tumor and other corresponding symptoms, including hematemesis, melena, persistent pain in the back and back radiating, jaundice, etc. (2). As_2O_3 can be used for the treatment of acute myeloid leukemia (3). It also inhibits the effects on other solid tumors by inhibiting cell proliferation and inducing apoptosis (4,5). As_2O_3 can inhibit VEGF protein expression in gastric cancer cells, inhibit new angiogenesis, and thus significantly inhibit the development of gastric cancer (6). As_2O_3 significantly induced apoptosis and inhibited proliferation in SGC7901 cells, which was mainly mediated by Bcl-2 conformational changes (7). In addition, in AFP-specific gastric cancer cell line FU97, the expressions of alpha-fetoprotein and STAT3 were involved in As_2O_3 induced apoptosis and inhibition of proliferation (8).

miRNA is a class of non-coding small molecule RNA consisting of 18-28 nucleotides whose main role is to participate in post-transcription protein expression regulation, and a large number of studies have shown that it can act on biological processes such as cell differentiation, cell cycle regulation and apoptosis (9). Among them, miR-885-5p has been reported to play an important role in cancer, including liver cancer, colorectal cancer, and osteosarcoma (10-12). miR-885-5p expression in liver cancer is negatively associated with tumor invasion and metastasis and total survival of cancer patients, and miR-885-5p overexpression in the cell system suppresses the cells by regulating Wnt/β-catenin signaling pathway (11). In patients with intrahepatic cholangiocarcinoma, miR-885-5p expression decreased significantly in intrahepatic cholangiocarcinoma tissues and its downregulation was positively associated with poor prognosis (13), suggesting that miR-885-5p plays an inhibitory role in tumor tissues. Further mechanism studies have found that miR-885-5p can be involved in regulating the proliferation of intrahepatic cholangiocarcinoma cells by binding to GALNT3 targeting to affect the activation of PI3K/Akt signaling pathway.

There were no unified current studies on its main mediating effects of tumor promotion or tumor suppression. Therefore, we intended to analyze the clinical efficacy of As_2O_3 in patients with gastric cancer to explore the mechanism how As_2O_3 can inhibit the proliferation of tumors through miR-885-5p.

Materials and Methods

Collection of patients

We included 52 normal people with outpatient physical examination from January 2019 to October 2020 in He Xian Memorial Hospital, China all of whom had no digestive tumors or diseases, no other internal chronic diseases. Overall, 52 patients with advanced gastric cancer were included in the same period, including 39 males and 13 females, aged 38-64 years old with the average age of 47.4 years old.

The inclusion criteria were: Patients with advanced gastric cancer confirmed by pathology; Patients and their family members agreed to participate in the study and agreed to follow-up. The patients were randomized into control group and As_2O_3 administration group. The control group was given oxaliplatin combined with tiggio regimen, in the dose of oxaliplatin 130 mg/m^2 each time + glucose injection 250 mL in light-proof intravenous drip, with tiggio 60mg/m^2 every day from the first day of the course of treatment, and orally twice in the morning and evening during 1-14 days of the course of treatment. As_2O_3 administration group was given As_2O_3 10 mg, 10% glucose injection 500 ml, 1 time/day, with intravenous infusion for 4 hours, which was treated for 2 weeks as 1 course, with 2 weeks of interval, a total of 2 courses. Clinical review and efficacy assessment were completed after 4 weeks of treatment.

This study has been approved by the Ethics Committee of He Xian Memorial Hospital, and informed consent was obtained from all patients.

Evaluation of Therapeutic Efficiency

According to the criteria for evaluating the short-term objective efficacy of solid tumors (14), patients were classified into complete remission (CR), partial remission (PR), no change (NC), and progressive disease (PD). The determination criteria were as follows. CR: the lesions accurately measured by spiral CT 10 mm completely disappeared and maintained for at least 4 weeks. PR: the product of the maximum diameter and the maximum vertical diameter of the tumor lesion reduced by more than 50% and maintained for more than 4 weeks. NC: the two-diameter product of tumor lesions decreased < 25% or increased < 25%, but no new lesions appeared. PD: the two-diameter product of tumor lesions increased > 25% or presented new lesions. The efficacy was evaluated according to objective response rate = (CR+PR)/total number of cases ×100% and benefit rate = (CR+PR+NC)/total number of cases ×100%.

Determination of miR-885-5p expression

All of the above incorporated peripheral venous blood 2ml (EDTA anticoagulant) were extracted and stored in a 4℃ refrigerator, and the blood samples were sent to the laboratory for qPCR. The total RNA was extracted with Trizol reagent (Invitrogen), and cDNA was synthesized through miRNA qRT-PCR SYBR (C10211-2, RiboBio) kit, which was amplified in the Exicycler 96 qPCR analyzer according to F: 5' TCCATTA CACTACCCTGCCTAT 3' and R: 5' CGCTAC-GTAACGGCATGACAGTG 3', with the following procedures: at 95℃ for 10min, at 95℃ for 10s, at 60℃ for 20s, and at 72℃ for 30s, for 40 cycles. Internal reference amplification sequence of U6 were F: 5' CTCGCTTCGG CAGCACA-TA 3' and R: 5' AAC GATTCACGAATTT-GCGT 3'. The relative expression quantity of miR-885-5p was calculated by $2^{-\Delta\Delta Ct}$.

Correlation analysis of miR-885-5p expression and tumor lesions

Pre- and post-treatment tumor lesion size data in control and As_2O_3 administration groups were obtained. Tumor tissue reduction rate (%) = (pre-treatment size - post-treatment size)/pre-treatment size *100%. The correlation between miR-885-5p expression in peripheral blood and the change of tumor size was determined by Pearson correlation analysis.

Culture of gastric cancer cell line

MGC-803 gastric cancer cell line was purchased from ATCC cell bank, and the cells were placed in DMEM cell nutrient solution (Gibco) containing 10% fetal bovine serum (Invitrogen) and 100U/ml penicillin / streptomycin (Sigma) and cultured in a 37 ℃ incubator with 5% CO_2.

MTT proliferation experiment

The cells were vaccinated in the 96-well plate, and As_2O_3 was added to the cells at appropriate concentrations of 0, 10, 20, 40, and 80 mol/L, respectively. After mixing, 20μl was added to each well to dilute to 5mg/ml CCK-8 (Solarbio) solution after training for 24 hours. After culture for 6 hours, the absorbance values were measured at 450nm and 600nm by ELISA. The cell activity was calculated, as well as cell proliferation rate (%) = (average OD in experimental group - average OD in blank control) / (average OD in control group - average OD in blank control) × 100%.

Regulation of miR-885-5p expression

When the density of MGC-803 cells increased to 40-60%, the cells were divided into blank control, inhibitor control, miR-885-5p inhibitor, mimics control and miR-885-5p mimics groups, where 1μl DMSO (Solarbio) and 1μl PBS buffer were added to the medium of blank control group. 100μl Opti-MEM (Invitrogen) was added to 1.5 ml EP tube, and then 5 μl Lipo2000 (Inretrogen) transdye agent, 50mM inhibitor control, miR-885-5p inhibitor, mimics control and miR-885-5p mimics (Shanghai Genepharma) were added respectively. The mixture was evenly mixed and incubated at room temperature for 20 min, and the mixed droplets were added into the cell culture medium for cell culture.

Prediction of miR-885-5p target gene

The binding of miR-885-5p to CDC73 target genes were predicted with target gene prediction software (Targetscan).

Fluoressin report trial

Fluoferase report test was conducted with 293T cells and dual luciferase reporter gene detection kit (complete gold). MiR-885-5p mimics, miR-885-5p NC and dual luciferase pmiRglo vectors were all purchased from Guangzhou Saicheng Biotechnology Co., Ltd. Relative light unit values of different samples were analyzed with dual luciferase reporting analysis system (PROMEGA).

Western blot (15)

RIPA pyrolysis (Solarbio) and the protease inhibitor PMSF (Solarbio) with a final concentration of 1 mM were added into cells of different groups. High-speed centrifugation was used to extract the total protein after fully cracking the cells. The concentration of the loading protein was adjusted to 5-10 μg/μL according to the total protein concentration obtained by quantification of BCA kit. SDS-PAGE separation gel was used for protein gel electrophoresis (15).

Statistical analysis

SPSS 23.0 software (IBM Corp., Armonk, NY, USA) was used to analyze the data results. The R×C Chi-square test was used to analyze the efficacy between the As_2O_3 treatment group and the control group in the treatment of advanced gastric cancer. The expression level of the two groups was compared by the independent sample *t* test, the expression level of miR-885-5p among multiple groups was analyzed by one-way ANOVA. Spearman correlation analysis was used to test the correlation between the expression of miR-885-5p and the size change of tumor lesion after As_2O_3 administration. $P<0.05$ was considered statistically significant.

Results

As2O3 treatment group was higher benefit rate than oxaliplatin combined with ticagio treatment group

After 4 weeks of treatment in As_2O_3 treatment and control groups, in control group and As_2O_3 administration group, the objective efficiency was 17.3% and 13.4%, respectively ($P= 0.8041$), and the benefit rate was 40.4% and 59.6% ($P =0.0493$) obtained by analyzed data (Table 1).

Table 1: Efficacy evaluation of As_2O_3 treatment group and control groups for advanced gastric cancer [case (%)]

Variable	*CR.*	*PR*	*NC*	*PD*	*CR + PR*	*CR + PR + NC*
As.$_2O_3$ Treatment Group (n=52)	0	9	12	31	9	21
Control Group (n=52)	0	11	21	20	11	32

Note: CR: complete remission; PR: partial remission; NC: no change; PD: progressive disease

miR-885-5p expression in peripheral blood was significantly increased in the gastric cancer group treated with As_2O_3

miR-885-5p expression in peripheral blood was significantly increased in the gastric cancer group treated with As_2O_3 ($P<0.001$) (Fig. 1A). In the normal population, miR-885-5p showed the same trend as patients in the gastric cancer group treated with As2O3, both of which were significantly higher than those in patients with gastric cancer ($P <0.001$). Pearson correlation analysis suggested that miR-885-5p expression was significantly positively correlated with the reduction of tumor tissue size after As_2O_3 administration ($r^2=0.48$, $P <0.001$) (Fig. 1B).

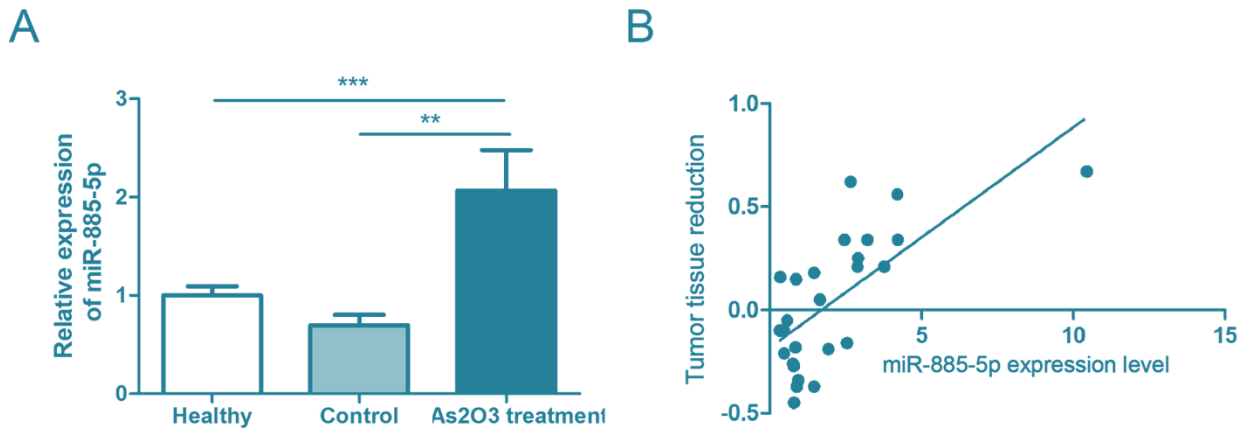

Fig. 1: miR-885-5p expression in peripheral blood was significantly increased in the gastric cancer group treated with As_2O_3

A. miR-885-5p expression in peripheral blood of normal population, control group and As2O3 treatment group was analyzed by qRT-PCR. B. Pearson correlation analysis confirmed that miR-885-5p expression was correlated with the change of tumor lesion tissue size after As2O3 administration. **, P <0.01;***, P <0.001

As_2O_3 could significantly reduce miR-885-5p expression and inhibit the proliferation of gastric cancer cells

The proliferation of MGC-803 cells was significantly inhibited with the increase of As_2O_3 concentration (Fig. 2A), and the IC50 value of As_2O_3 at 48h was 40 μmol/L. The specific mechanism of As_2O_3 affecting the proliferation of gastric cancer cells was further explored through the qRT-PCR experiment. As_2O_3 could reduce miR-885-5p expression (P =0.0257) (Fig. 2B).

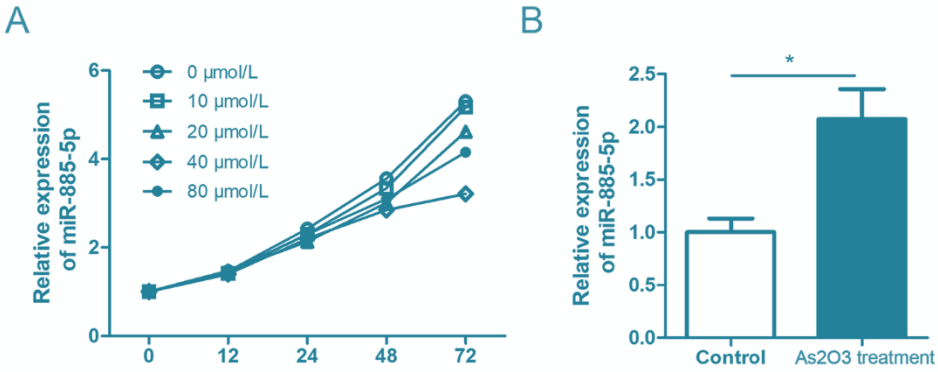

Fig. 2: As_2O_3 could significantly reduce miR-885-5p expression and inhibit the proliferation of gastric cancer cells

A: Effects of different As_2O_3 concentrations on the proliferation of gastric cancer cells were investigated by CCK-8. B: miR-885-5p expression in gastric cancer cells of control group and 40μmol/L As_2O_3 treatment group was detected by qRT-PCR. *, P <0.05

miR-885-5p specifically regulated CDC73 expression in gastric cancer cells

miR-885-5p might target the binding CDC73 gene site (Fig. 3A), similarly validated by luciferase reported gene experiments (Fig. 3B).

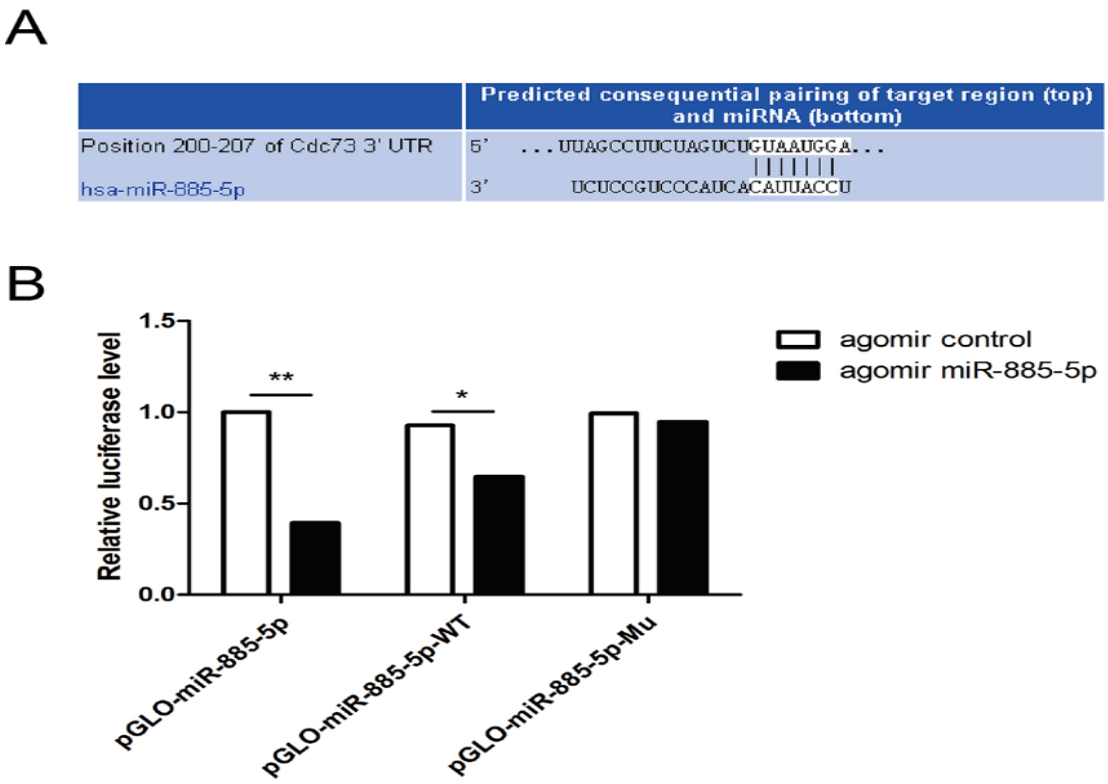

Fig. 3: miR-885-5p specifically regulated CDC73 expression in gastric cancer cells
A: TargetScan Bioinformation Analysis website predicted that miR-885-5p might target binding genes. B: Bilucifer-ase reporting experiment experimentally demonstrated a targeted binding relationship between miR-885-5p and CDC73.
*, P <0.05;**, P <0.01

miR-885-5p affected the proliferation of gastric cancer cells through the targeted regulation of CDC73 expression

By transfecting miR-885-5p mimics and inhibitor overexpression and knocking down miR-885-5p expression, the results of qRT-PCR (Fig. 4A) and Western blot (Fig. 4B-4C) demonstrated a significantly reduced CDC73 expression. CDC73 siRNA was further transfected into the miR-885-5p inhibitor group, and the knockdown of CDC73 could significantly reverse the enhanced proliferation effect of gastric cancer cells mediated by miR-885-5p inhibitor (Fig. 4D), suggesting that miR-885-5p affected gastric cancer cell proliferation by regulating CDC73 expression.

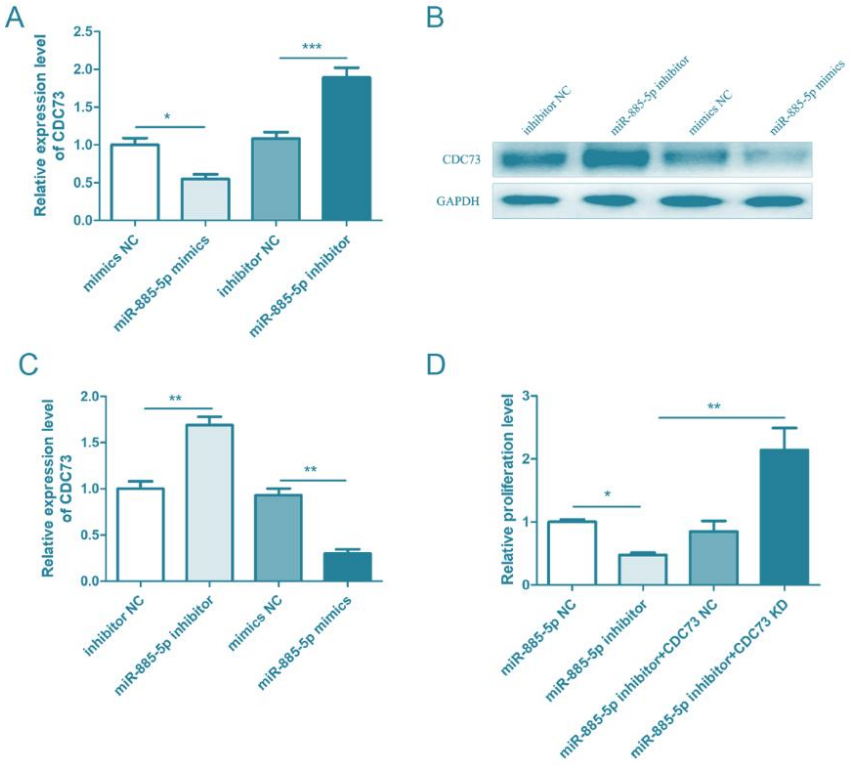

Fig. 4: miR-885-5p affected the proliferation of gastric cancer cells by targeting CDC73 expression
A: Effects of different groups on CDC73 mRNA expression under the regulation of miR-885-5p expression were detected by qRT-PCR. B-C:Western blot investigated the influence of miR-885-5p regulation on CDC73 protein expression. D: Effects of reduced miR-885-5p expression and low CDC73 knockdown on the proliferation of gastric cancer cells were investigated. *, P <0.05, **, P <0.01;***, P <0.001

Discussion

Gastric cancer is one of the most common gastrointestinal malignancies in the world, with high morbidity and mortality and very low 5-year survival rate. Over the past decade, some cancer drugs have been approved for cancer treatment. Arsenic trioxide (As_2O_3) is an earlier drug used for tumor treatment. It could bind to PML-RARα specificity, leading to its degradation, mediating partial differentiation of leukemia premyelocytes and inducing apoptosis (16). It is mainly used in the research and treatment of blood system tumors such as acute myeloid leukemia (4), which can greatly improve the remission and survival rate of patients with acute premyelogenous leukemia. After confirming As_2O_3 as a drug for leukemia, especially APL, there were increasing evidence suggest that the efficacy of As_2O_3 is not limited to blood disease. As_2O_3 can also induce apoptosis and growth block in a variety of solid tumor cell lines, such as pancreatic, prostate, liver cancer, bladder migration, and breast cancer (17,18). In nude rats, the addition of As_2O_3 at 2.5 mg/kg results in about 30% decrease in tumor growth, and that at 5 mg/kg can result in a tumor growth volume decrease about 50% (5). All above evidence suggest that As_2O_3 can participate in the occurrence and development of gastric cancer, and mainly play an anti-cancer role.

As_2O_3 can inhibit the proliferation of lung cancer cells, reduce the size of tumor formation, and reduce the expression of stem cell biomarker CD133 and transcription factors such as SOX2 and OCT4 (19). Similarly, As_2O_3 in breast cancer can also inhibit the cell growth by upregulating Let-7a expression (20). Furthermore, As_2O_3 can assist in the treatment of liver cancer by increasing the number of T lymphocytes in local lesions and reducing the effect of Treg cell infiltration on

the immune microenvironment (21). As_2O_3 also affects cell apoptosis in gastric cancer (22), and inhibits cell migration by regulating the expression of MMP-2 signaling pathway in gastric cancer cells (23). As_2O_3 in the human gastric cancer cell line SGC7901 helped transform the cell protection phenotype of Bcl-2 cell line into cell destruction type, thus showing its cytotoxic effects (6). Through internal and external experiments As_2O_3 can inhibit tumor growth by inhibiting the formation of new blood vessels, mainly by inhibiting the expression of VEGF protein (5). However, the specific mechanism of As_2O_3 regulating the progression of gastric cancer remains to be further studied.

miR-885-5p plays an important role in cancer progression. In hepatocellular carcinoma, miR-885-5p expression was negatively associated with cancer invasion and metastasis ability, and poor survival in cancer patients (24). Moreover, miR-885-5p overexpression can inhibit the malignant behavior of hepatocyte cancer cells by regulating Wnt/ β-catenin signaling pathway. miR-885-5p promotes the progression of colon cancer tumors by targeting cytokinine signaling pathway inhibitors (12). In addition, thyroid papilloma suggests that miR-885-5p can be regulated by hsa_circ_0004458, to activate RAC1 protein expression, so as to promote tumogenesis (25). However, no consensus has been reached on the role of miR-885-5p in gastric cancer. miR-885-5p promotes the proliferation and invasion of gastric cancer by regulating YPEL1 (26), while Jiang et al. (27) found that miR-885-5p targeted ME1 to inhibit the invasion and metastasis of gastric cancer. In this regard, the results of this study found that miR-885-5p significantly highly expressed in peripheral blood in patients treated with As_2O_3, which also decreased in patients with gastric cancer compared with normal people, indicating that miR-885-5p plays an important role in the development of gastric cancer and As2O3-mediated anti-tumor therapy.

miRNA is well known to regulate gene expression by binding to target genes in the 3' -UTR region. Thus, similar to many other miRNAs, bioinformatics prediction results showed that miR-885-5p can specifically bind to target gene CDC37, and its targeted regulatory effect was also verified by qRT-PCR and Western blot. CDC37 is barely expressed in normal prostate tissue, with the highest proportion of CDC37-positive cells in moderately differentiated prostate cancer, and has been confirmed to be a HSP90 kinase-specific partner. Specific inhibition of HSP90 kinase can be achieved by blocking its interaction or directly inhibiting CDC37, and the development of small molecule inhibitors targeting HSP90-CDC37 is another effective strategy for implementing cancer treatment (28,29). Our data showed that miR-885-5p can affect cell proliferation by inhibiting CDC37.

Conclusion

As_2O_3 might be used in the clinical treatment of gastric cancer, and its main mechanism is to regulate miR-885-5p expression in patients with gastric cancer, targeting CDC37 expression of gastric cancer cells. However, there are still some shortcomings in this paper, and more patients with gastric cancer should be collected in subsequent research for randomized controlled experiments to statistically analyze the possibility of As_2O_3 for the clinical treatment of gastric cancer.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interest.

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