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LncRNA GIHCG regulates microRNA-1281 and promotes malignant progression of breast cancer

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Abstract. – OBJECTIVE: This study aimed to investigate the expression characteristics of long non-coding RNA (lncRNA) GIHCG in breast cancer (BCa), and further investigate its role in BCa and its relationship with clinical characteristics and prognosis.

PATIENTS AND METHODS: Quantitative Real Time-Polymerase Chain Reaction (qRT-PCR) was performed to examine GIHCG expression in 53 pairs of BCa tumor tissues and adjacent tissues. The interaction between the level of GIHCG and the clinical indicators of BCa and the prognosis of patients was then analyzed. Lentivirus was transfected into BCa cell lines to construct the GIHCG knockdown model. The cell counting kit-8 (CCK-8), cell cloning, and 5-Ethynyl-2'-deoxyuridine (EdU) assays were performed to analyze the influence of GIHCG on the biological function of BCa cells, as well as to explore whether it could play a role *via* modulating microRNA-1281.

RESULTS: QRT-PCR results showed that the GIHCG level was remarkably higher in the BCa tumor tissue than in adjacent ones. Compared with patients with low expression of GIHCG, patients with high expression of GIHCG had higher pathological grades and a lower overall survival. Besides, the proliferation ability of BCa cells in GIHCG knockdown group was significantly decreased compared with NC group. QRT-PCR results indicated that silencing GIHCG increased the expression of miR-1281, thereby promoting the malignant progression of BCa. Also, the silence of miR-1281 reversed the effect of GIHCG on the proliferative capacity of BCa, thus increasing the cell anti-apoptotic ability.

CONCLUSIONS: GIHCG levels were remarkably increased in both BCa tissues and cells, which was related to the pathological stage and poor prognosis of BCa patients. Besides, GIHCG might promote the malignant progression of BCa by inhibiting microRNA-1281.

Key Words:
LncRNA GIHCG, MicroRNA-1281, Breast cancer, Malignant progression.

Introduction

Breast cancer (BCa) is the most common female malignant tumor worldwide[1,2]. According to the latest annual tumor statistics in the United States, 252,710 new cases of BCa were expected in the United States in 2017, accounting first in the incidence of female malignant tumors, and 40,610 people would die of BCa, ranking second in the death of female malignant tumors[3,4]. BCa is also the most common malignant tumor among Chinese women and has seriously threatened the health and life safety of Chinese women[5,6]. In the past decades, the development of surgery, chemotherapy, radiotherapy, endocrine therapy, and molecular targeted therapy has markedly improved the treatment effect of BCa, while there are still many challenges in the diagnosis and treatment of BCa[7,8]. To overcome these problems in the process

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of current research on BCa, a better understanding of the molecular mechanism and regulatory network in BCa from gene level will be of great importance. This is also necessary to establish novel and effective therapeutic techniques and to find biomarkers with prognostic value[9].

Long non-coding RNAs (lncRNAs) have been a hotspot of research in recent years. It is a class of non-coding RNAs with more than 200 nucleotides in length, while rarely has the protein-coding function. LncRNA was once considered the "dark matter" of gene transcription. However, it has been found[10-12] that lncRNA has critical biological functions, such as regulating cell proliferation, cell cycle, cell differentiation, apoptosis, etc. Also, abnormal expression of lncRNA is closely related to human diseases, especially in tumor[13,14]. A variety of lncRNAs have been involved in the occurrence, growth, infiltration, metastasis, and recurrence of gastric cancer, lung cancer, prostate cancer, and other tumors[15,16]. Therefore, lncRNAs play the role of oncogenes or tumor suppressors in the regulation of tumors. The in-depth study of tumor-associated lncRNAs will definitely promote the elucidation of the molecular regulation mechanism of tumor development, invasion, and metastasis from a new perspective. This would also make the current revolutionary changes in the understanding of cellular structural networks and regulatory networks[17,18].

Compared with miRNAs that have been extensively studied in the past, lncRNAs still belong to a relatively unknown field[19]. Currently, researches on lncRNAs in BCa are still rare. Although several lncRNAs have been found to be associated with BCa, the regulation mechanisms of most lncRNA molecules are still not precise. It is still necessary to continue to search for lncRNAs that are abnormally expressed in breast cancer and to further explore their molecular biological mechanisms underlying breast cancer[20,21]. Based on the above characteristics, this study mainly focused on whether GIHCG was a potential serological marker for early diagnosis of tumors, and whether it can provide a viable option for target gene therapy of tumors. Here, we predicted that GIHCG could be involved in the process of BCa cell proliferation by targeting and regulating microRNA-1281.

Patients and Methods

Patients and BCa Samples

Tumor specimens and adjacent ones of 53 BCa patients ranging in age from 31 to 88 years old were collected and stored in a refrigerator at –80°C. All specimens were diagnosed by two high-grade deputy director pathologists. Patients and their families had been fully informed, and informed consent had been signed and approved by the Ethics Oversight Committee.

Cell Lines and Reagents

The human BCa cell lines (MCF-7, MDA-MB-231, MDA-MB-435S, and SKBR3) and normal mammary epithelial cell line, MCF-10A were purchased from American Type Culture Collection (ATCC; Manassas, VA, USA). Both Dulbecco's Modified Eagle's Medium (DMEM) medium and fetal bovine serum (FBS) were purchased from Life Technologies (Gaithersburg, MD, USA). All cells were cultured in a DMEM high glucose medium containing 10% FBS, penicillin (100 U/mL), and streptomycin (100 μg/mL) in a 37°C incubator with 5% CO_2. When growing to 80%-90% confluence, the cells were digested with 1×trypsin+ ethylenediaminetetraacetic acid (EDTA).

Transfection

Control group (sh-NC) and the knockdown GIHCG lentiviral sequence (sh-GIHCG) were purchased from the Shanghai Jima Company (Shanghai, China). Cells were plated in 6-well plates and grown to a cell density of 70%. Then, lentiviral transfection was performed according to the manufacturer's instructions. Cells were harvested 48 h later for quantitative Real Time-Polymerase Chain Reaction (qRT-PCR), Western blot analysis, and cell function experiments.

Cell Proliferation Assay

The cells after 48 h of transfection were harvested and plated into 96-well plates at 2000 cells per well. Cells were cultured for 6, 24, 48, and 72 h respectively, and then added with Cell Counting Kit-8 (CCK-8; Dojindo Laboratories, Kumamoto, Japan) reagent. After incubation for 2 h, the optical density (OD) value of each well was measured in the microplate reader at 490 nm absorption wavelength.

Colony Formation Assay

After 48 h of transfection, cells were collected, and 200 cells were seeded in each well of a 6-well plate and cultured in complete medium for 2 weeks. The medium was changed after one week. Then, twice a week. After 2 weeks, the cells were cloned and then washed twice with phosphate-buffered saline (PBS). The cells were fixed in 2 ml of methanol for 20 min. After the

methanol was aspirated, cells were stained with 0.1% crystal violet staining solution for 20 min, washed 3 times with PBS, photographed, and counted under a light-selective environment.

Ethynyl-2′-Deoxyuridine (EdU) Proliferation Assay

To demonstrate the ability of GIHCG to proliferate in BCa cells, the EDU proliferation assay (RiboBio, Nanjing, China) was performed according to the manufacturer's requirements. After transfection for 24 h, the cells were incubated with 50 μm EDU for 2 h. Then, stained with AdoLo and 4',6-diamidino-2-phenylindole (DAPI), and the number of EDU-positive cells was detected by fluorescence microscopy. The display rate of EDU positive was shown as the ratio of the number of EDU positive cells to the total DAPI chromogenic cells (blue cells).

QRT-PCR

Total RNA was extracted from BCa cell lines and tissues using TRIzol reagent (Invitrogen, Carlsbad, CA, USA), and RNA was reverse transcribed into cDNA using Primescript RT Reagent (TaKaRa, Otsu, Shiga, Japan). The qRT-PCR reaction was carried out using SYBR® Premix Ex Taq™ (TaKaRa, Otsu, Shiga, Japan), and StepOne Plus Real-time PCR System (Applied Biosystems, Foster City, CA, USA). Data analysis was performed using ABI Step One software and the relative levels of mRNA were calculated using the $2^{-\Delta\Delta Ct}$ method. Primer sequences used were as follows: GIHCG, F: 5'-GCGAGCAGCGCAACTACTTGCTC-3', R: 5'-GGCAGGCATATGAAGCGA-3'; microRNA-1281, F: 5'-GTCACGTACCATCGCGTCAGAG-3', R: 5'-GACCGCTGTCCTGGCGAACG-3'; U6: F: 5'-GCTTCGGCAGCACATATACTAAAAT-3', R: 5'-CGCTTCAGAATTTGCGTGTCAT-3'; GAPDH: F: 5'-CGCTCTCTGCTCCTCCTGTTC-3', R: 5'-ATCCGTTGACTCCGACCTTCAC-3'.

Statistical Analysis

Statistical analysis was performed using GraphPad Prism 5 V5.01 Software (La Jolla, CA, USA). Statistical differences between the two groups and multiple groups were analyzed using Student's *t*-test and one-way analysis of variance (ANOVA) followed by Post-Hoc Test (Least Significant Difference), respectively. Independent experiments were repeated at least three times for each experiment, and the data were expressed as mean ± standard deviation. $p < 0.05$ was considered statistically significant.

Results

GIHCG was Highly Expressed in BCa Tissues and Cell Lines

To determine the role of GIHCG in BCa, we collected a total of 53 pairs of BCa tumor tissue specimens and adjacent ones. The expression of GIHCG in the above tissues was examined using qRT-PCR. The results revealed that GIHCG expression was higher in BCa tumor tissues than in adjacent ones (Figure 1A). Besides, the study also demonstrated that GIHCG expression was higher in patients with T3-4 stage BCa than in those with T1-2 stage BCa (Figure 1B). At the same time, GIHCG level in BCa cell lines was found remarkably higher than that in the normal breast tissue cell MCF-10A, especially in MDA-MB-231 and SKBR3 cell lines (Figure 1C). These results suggested that GIHCG might play a role as a tumor-promoting gene.

GIHCG Expression Was Correlated with Pathological Stage and Overall Survival in BCa Patients

According to the GIHCG expression, 53 pairs of tissue samples were divided into high and low expression group. Chi-square test was used to analyze the interplay between GIHCG expression and age, pathological stage, lymph node or distant metastasis of BCa patients. As shown in Table I, GIHCG high expression was positively correlated with BCa pathological stage. Also, the Kaplan-Meier survival curve revealed that high expression of GIHCG was remarkably associated with poor prognosis of BCa. The higher the level of GIHCG, the worse the prognosis ($p<0.05$; Figure 1D). These results demonstrated that GIHCG level was correlated with pathological stage and overall survival in BCa patients.

Knockdown of GIHCG Inhibited Cell Proliferation in BCa Cells

To explore the influence of GIHCG on the proliferation of BCa cells, we successfully constructed the sh-GIHCG model and the transfection efficiency was verified using qRT-PCR (Figure 2A). Subsequently, CCK8, cell clones, and EdU assays were performed to analyze cell proliferation in NC and sh-GIHCG groups. As a result, we found that the proliferation rate of BCa cells in the latter group was remarkably decreased (Figure 2B-2D).

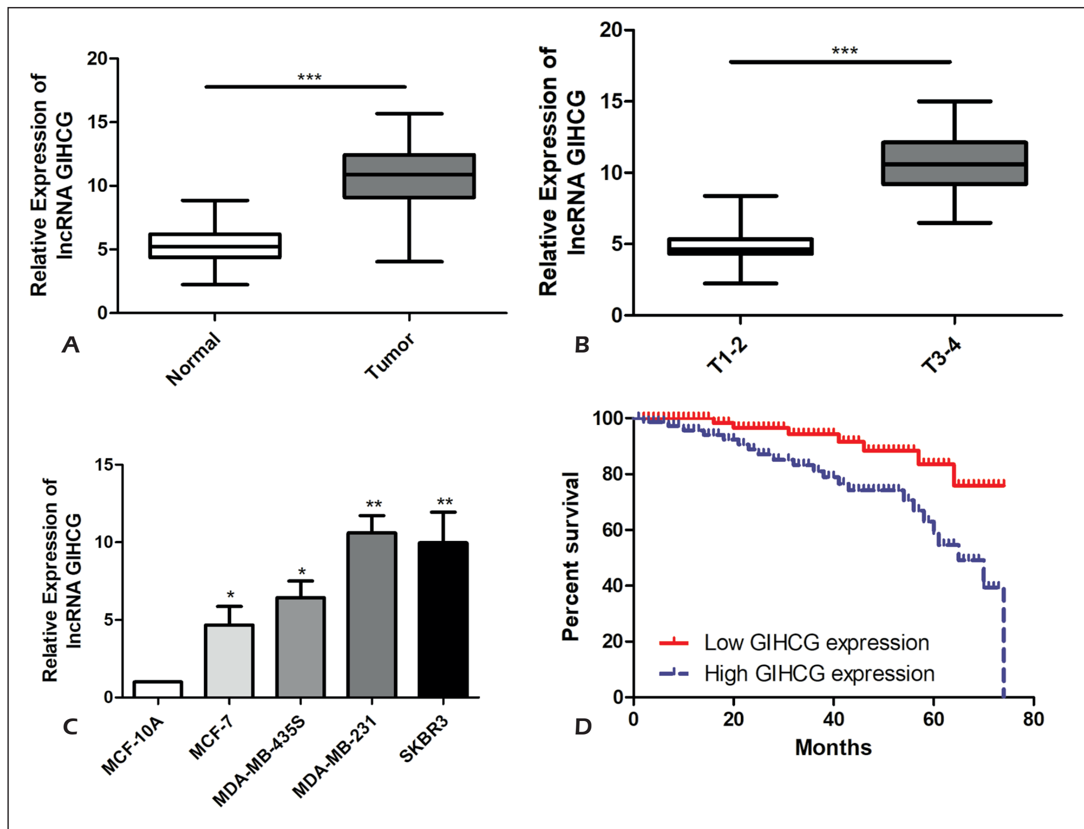

Figure 1. High expression of GIHCG in breast cancer tissues and cell lines. **A**, QRT-PCR was used to detect the expression of GIHCG in breast cancer tissues and adjacent tissues; **B**, QRT-PCR was used to detect the expression of GIHCG between T1-2 and T3-4 in histopathological grades of breast cancer; **C**, QRT-PCR was used to detect the expression level of GIHCG in breast cancer cell lines; **D**, Kaplan Meier survival curve of breast cancer patients based on GIHCG expression; The prognosis of patients with high expression was significantly worse than that of low expression group. Data are mean ± SD, *p<0.05, **p<0.01, ***p<0.001.

MicroRNA-1281 was Lowly Expressed in BCa Tissues and Cell Lines

TargetScan, miRbase, and MiRcode databases were applied to assess the potential relation between lncRNAs and miRNAs. Bioinformatics analysis suggested four miRNAs as potential targets of GIHCG (Figure 3A). Subsequently, qRT-PCR was used to detect the difference in expres-

Table I. Association of lncRNA GIHCG expression with clinicopathologic characteristics of breast cancer.

Parameters	No. of cases	GIHCG expression		*p*-value*
		Low (%)	High (%)	
Age (years)				0.630
<60	24	14	10	
≥60	29	15	14	
T stage				0.008
T1-T2	26	19	7	
T3-T4	27	10	17	
Lymph node metastasis				0.254
No	22	10	12	
Yes	31	19	12	
Distance metastasis				0.094
No	33	21	12	
Yes	20	8	12	

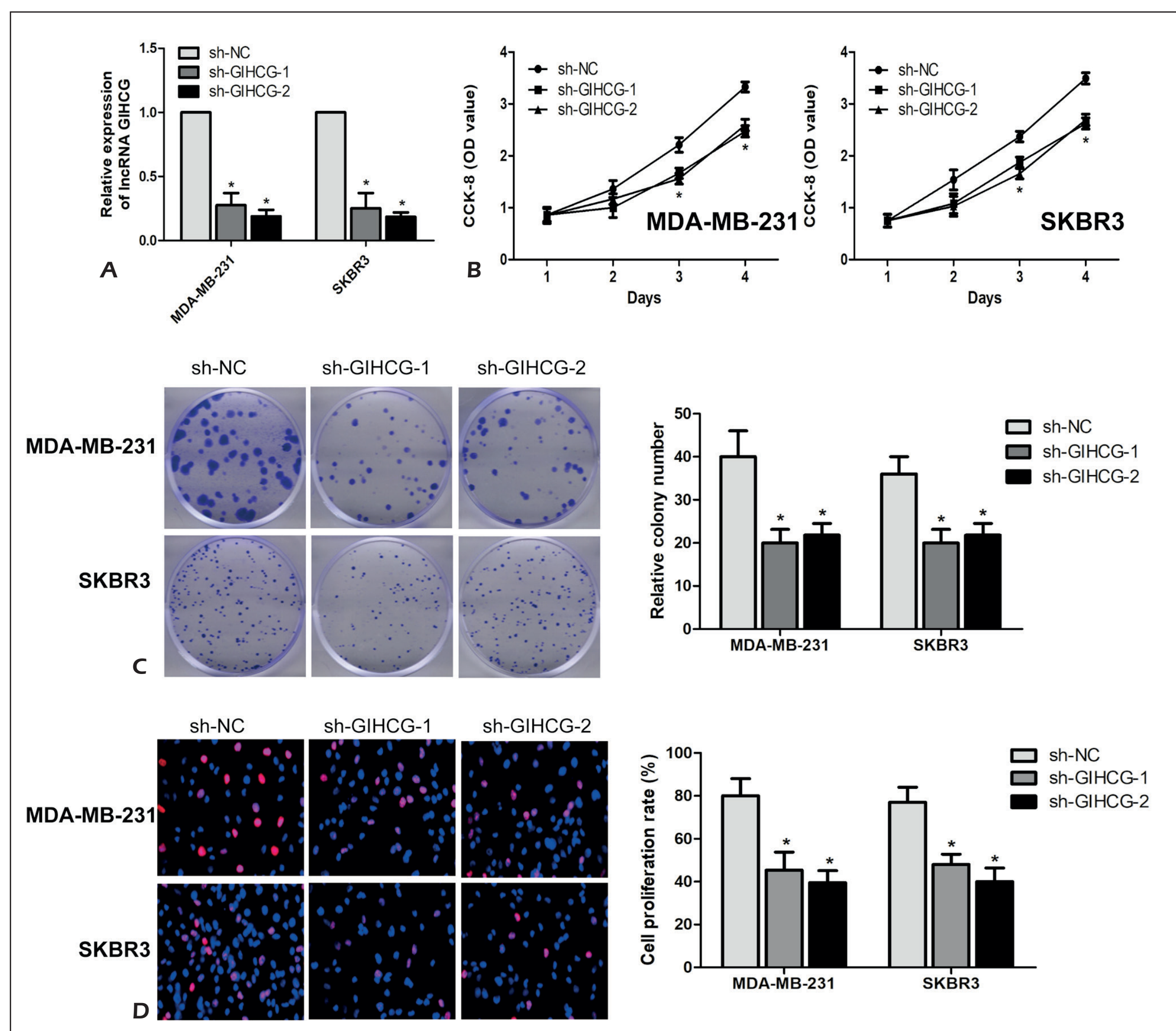

Figure 2. Inhibition of breast cancer cell proliferation after silencing GIHCG. **A**, QRT-PCR verified the interference efficiency after small interference transfection of GIHCG in MDA-MB-231 and SKBR3 cell lines; **B**, CCK-8 assay detected the effect of interference with GIHCG on breast cancer cell proliferation in MDA-MB-231 and SKBR3 cell lines; **C**, Cell cloning assay detected the ability of breast cancer cell clones to interfere with GIHCG in MDA-MB-231 and SKBR3 cell lines (magnification × 40); **D**, EdU assay detected the effect on breast cancer cell proliferation after interfering with GIHCG in MDA-MB-231 and SKBR3 cell lines (magnification × 40). Data are mean ± SD, *$p<0.05$.

sion of the four potential miRNAs in sh-NC group and sh-GIHCG group. The difference in microRNA-1281 expression was found to be the most significant. Therefore, it was suggested that there might be an association between GIHCG and microRNA-1281(Figure 3B).

In this study, microRNA-1281 expression was found remarkably down-regulated in BCa tissues compared with adjacent normal ones (Figure 3C). In addition, GIHCG and microRNA-1281 levels showed a negative correlation in BCa tissues (Figure 3D).

GIHCG Modulated MicroRNA-1281 Expression in BCa

To further explore the interaction between GIHCG and microRNA-1281, microRNA-1281 was silenced in BCa cell lines knocked down GIHCG to investigate their role in BCa (Figure 4A). Subsequently, CCK-8, plate cloning, and EdU experiments confirmed that microRNA-1281 could counteract the proliferative effect of GIHCG on BCa cells (Figure 4B-4D), suggesting that GIHCG could modulate microRNA-1281 expression in BCa.

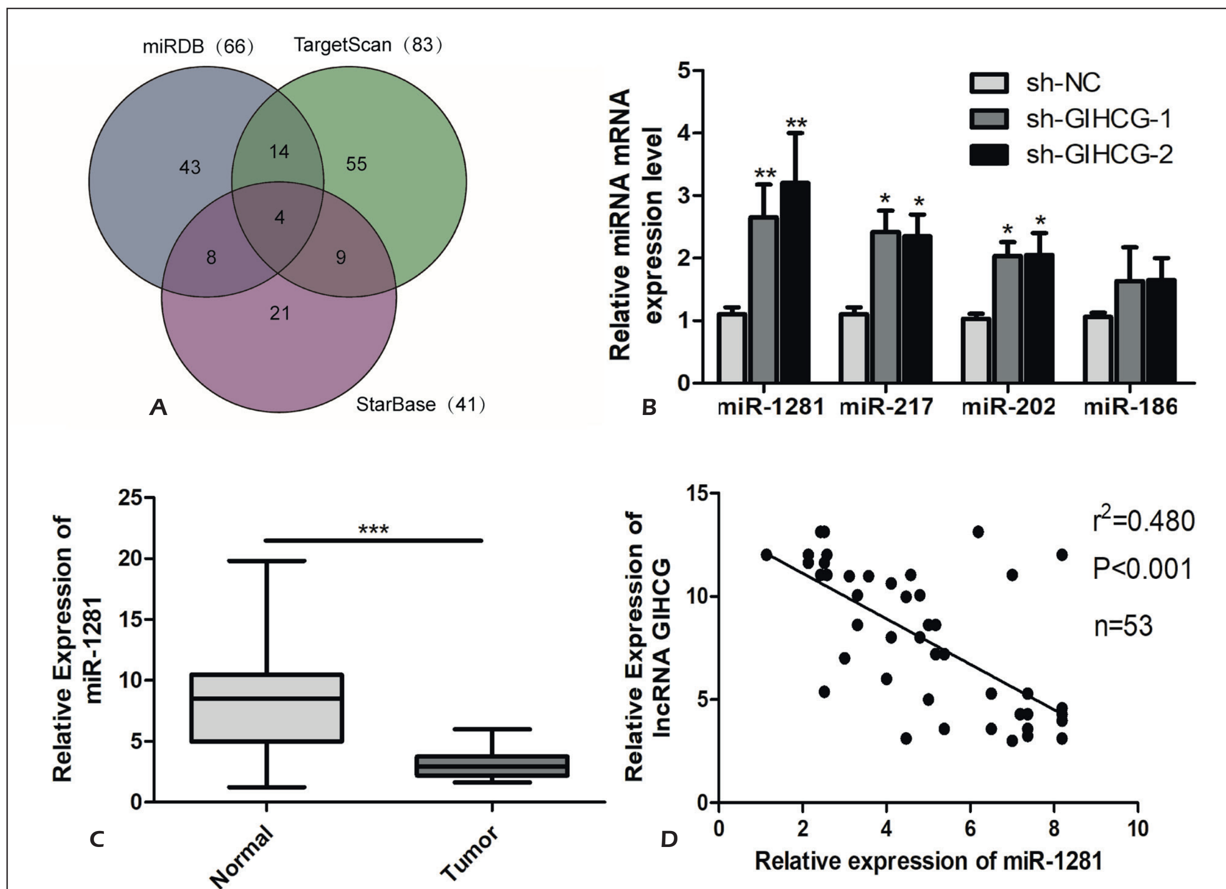

Figure 3. Direct targeting of miR-1281 by GIHCG. **A**, TargetScan, miRbase, and MiRcode suggest that GIHCG targets the bound miRNA; **B**, Potential miRNA expression after silencing GIHCG, with miR-1281 being the most apparent; **C**, QRT-PCR was used to detect the differential expression of miR-1281 in breast cancer tissues and adjacent tissues; **D**, There was a significant negative correlation between the ex-pression levels of GIHCG and miR-1281 in breast cancer tissues. Data are mean ± SD, *p<0.05, **p<0.01, ***p<0.001.

Discussion

Transcriptome refers to the sum of all RNAs that are transcribed from a particular tissue or cell, including mainly mRNA and lncRNA[9,10]. The central principle indicates that the genetic information of an organism is transferred from DNA to RNA and then from RNA to protein, which is the process of transcription and translation of genetic information[10]. Since the "post-genome" era, high-throughput second-generation sequencing technology and gene chip technology have developed rapidly. Bioinformatics in the transcription splicing and assembly, quantitative comparison and reference sequence transcript expression have achieved great progress, which makes the system comprehensive disease of transcription for possible[9]. Especially in the field of tumor molecular mechanism research, systematically and comprehensively studying the transcriptome information of malignant tumors, elucidating the regulation law of gene expression and constructing the gene regulation network have become a hot spot in the field of tumor research at present[11,12].

Human genome studies have found that only about 1% of genes can be transcribed into biologically functional RNA. While most of the RNAs have no protein-coding function and was considered as the by-products of transcription or "dark matter" in the genome[11-14]. LncRNAs are universally transcribed in eukaryotic cells and were once considered to have no biological function. However, accumulated studies have shown that lncRNA can play a role in regulating cell methylation, histone modification, chromatin remodeling, mRNA degradation, protein modification, and miRNA precursors[15,16]. Besides, abnormal expression of lncRNA is closely relat-

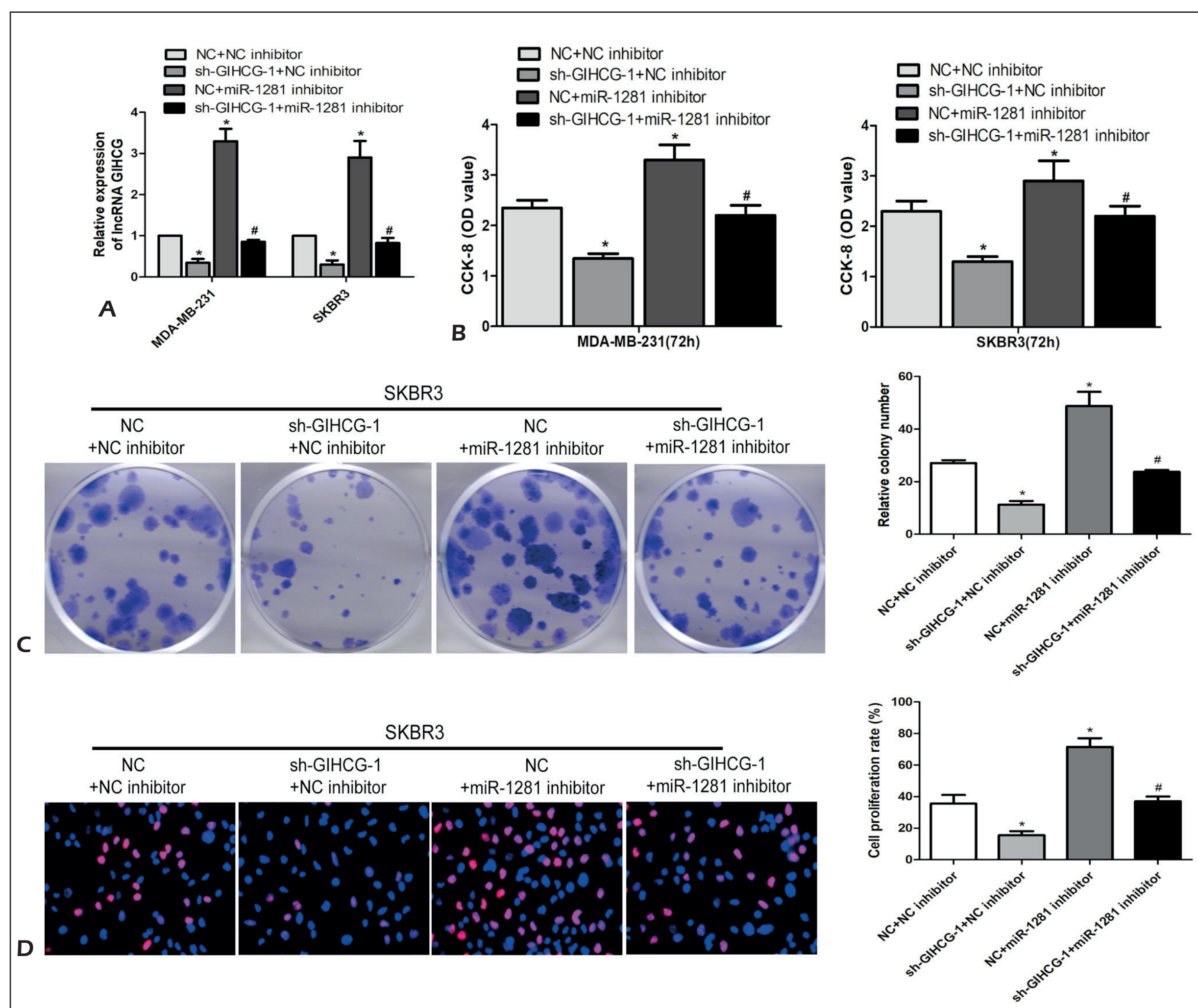

Figure 4. GIHCG regulates the mechanism of action of miR-1281 in breast cancer cells. **A**, QRT-PCR verified GIHCG expression levels after co-transfection of GIHCG with miR-1281 in MDA-MB-231 and SKBR3 cell lines; **B**, CCK-8 assay detected the effect of co-transfection of GIHCG and miR-1281 on breast cancer cell proliferation in MDA-MB-231 and SKBR3 cell lines; **C**, Cell cloning assay detected the ability of GIHCG and miR-1281 to co-transfect to form breast cancer cell clones in the SKBR3 cell line (magnification × 40); **D**, EdU assayed the effect of co-transfection of GIHCG and miR-1281 on breast cancer cell proliferation in SKBR3 cell line (magnification × 40). Data are mean ± SD, *#p<0.05.

ed to human diseases, especially in the field of tumor research[17]. Currently, abnormal expression of GIHCG has been found in a variety of tumors and might be associated with the malignant progression of tumors[22,23]. In our study, the role of GIHCG in the development and progression of BCa was first explored by using a large number of BCa clinical specimens. We found that GIHCG expression in BCa tissue and BCa cell line had a different degree of increase, suggesting that GIHCG might play an important role in the process of the development of BCa. To verify the effect of GIHCG on the biological behavior of BCa cell lines, GIHCG knockout model was constructed. Then, the CCK8 assay, cell cloning experiments, and EdU detection were performed. The results showed that GIHCG can promote the proliferation of BCa, while its specific molecular mechanism was unclear.

Abnormally expressed lncRNAs play a pivotal role in a variety of tumors. However, the molecular mechanism by which these lncRNAs affect tumor formation and/or progression is still unclear[19-21]. Some researches[13,18] have shown that the regulation mechanisms of lncRNA are complex and diverse and were investigated mainly *via* regulating the down-

stream miRNA expression. Therefore, the study on the occurrence and regulation mechanism of BCa is of great significance for finding the target targets for the treatment of BCa, especially the metastasis of tumor cells[9,10]. In this work, to clarify whether GIHCG promoted the incidence and development of BCa by regulating microRNA-1281, the expression of microRNA-1281 was detected by qRT-PCR after the knockdown of GIHCG. Our results indicated that microRNA-1281 was remarkably up-regulated after the knockdown of GIHCG, indicating that GIHCG might promote the proliferation of BCa through microRNA-1281. Subsequently, to explore whether or not GIHCG can promote the malignant progression of BCa by regulating microRNA-1281, we performed a recovery experiment and found that microRNA-1281 could reverse the malignant progression of BCa caused by the knockdown of GIHCG. With the deepening of research, a further understanding of the biological functions of genes and their roles in the development and progression of tumors will be more conducive to the diagnosis, treatment, and prognosis evaluation of tumors.

Conclusions

We first indicated that GIHCG expression was remarkably increased in BCa and was associated with BCa pathological stage and poor prognosis. Besides, GIHCG might promote the proliferation of BCa by regulating microRNA-1281.

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Conflict of Interests

The Authors declared that they have no conflict of interests.

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