Original Research Paper

Clinical Significance of Precise Hyperthermic Intraperitoneal Chemotherapy Up-regulation RP11-356I2.2 Restraining the Occurrence and Development of Gastric Cancer

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Abstract: In order to study the therapeutic effect and possible mechanism of Precise Hyperthermic Intraperitoneal Chemotherapy (HIPEC) on gastric cancer, the expression of RP11-356I2.2 in gastric cancer cell lines and tissues was detected by real-time fluorescence quantitative PCR (RT-PCR). Chi-square test was used to analyze the correlation between the expression and clinic pathological parameters. Western blotting was used to detect the expression of RP11-356I2.2 and tumor suppressor geneKLF17 after precise HIPEC. The effect of RP11-356I2.2 on KLF17 protein was observed and expressed by Western blotting and immunofluorescence. COX regression model was used to analyze the relationship between the expression of RP11-356I2.2 and KLF17 and the prognosis of patients with gastric cancer. The results of RT-PCR showed that RP11-356I2.2 was lower in BGC-823, MKN-28, MGC-803, SGC-7901 and MKN-45 than normal stomach cells GES-1 ($P<0.05$). Its expression level was inversely proportional to the malignant degree of gastric cancer. Meanwhile, stable expression SGC-7901/RP11-356I2.2 cell line was established, western blotting and immunofluorescence showed the up-regulation of KLF17 protein. The expression of RP11-356I2.2 and tumor suppressor gene KLF17 increased after precise HIPEC. After 5 years of follow-up, the Disease-Survival rate (DFS) and total Survival rate (OS) of KLF17 high expression group were 9.7 and 14.2 months respectively, which were significantly longer ($P<0.05$) than KLF17 low expression group, DFS (5.4 months) and OS (10.2 months). The up-regulation of KLF17 protein by up-regulation of RP11-356I2.2 in precise intraperitoneal hyperthermic chemotherapy may be one of the mechanisms of HIPEC inhibiting gastric cancer.

Keywords: Long Noncoding RNA, RP11-356I2.2, Gastric Cancer

Introduction

According to the statistics of cancer mortality in 185 countries by the International Cancer Research Institute, gastric cancer ranks the third in all cancer mortality, about 8.2% (Bray *et al*., 2018). Gastric cancer is the second leading cause of cancer mortality in China. There are about 460000 new cases each year and more than 80% of them are advanced gastric cancer. Even after radical resection or chemotherapy or even targeted therapy, patients will still have tumor recurrence or distant metastasis (Zong *et al*., 2016). Unrespectable advanced or metastatic gastric cancer is still a disease difficult to control, with a poor median survival rate (Nienhüser and Schmidt, 2018). The metastasis of gastric cancer is usually direct invasion and lymphatic metastasis. In the late stage, hematogenous metastasis or intraperitoneal implant metastasis may also occur. Ribeiro (1998) reported that almost 100% of patients with gastric cancer who found FCC positive in the peritoneal free cancer cells during subtotal mastectomy would have peritoneal implant metastasis. More than 70% of advanced gastric cancer patients died of peritoneal implant metastasis (Geng *et al*., 2016). Scholars at home and abroad have made unremitting efforts to inhibit the invasion and metastasis of gastric

cancer. So far, the recurrence and metastasis of postoperative chemotherapy of gastric cancer has not been effectively resolved.

At present, it has been proved that hyperthermia can inhibit the invasion and metastasis of malignant tumors and enhance the sensitivity of radiotherapy and chemotherapy (Fang *et al.*, 2019; Jin *et al.*, 2018). However, most of the literatures do not elaborate on the equipment used or the technical methods adopted. In the past, single intraperitoneal perfusion or thermal therapy equipment with low accuracy of temperature control were mostly used in our country, which made its effectiveness and safety not be fully guaranteed. The further clinical application was limited. High-Precision hypothermic intraperitoneal Chemotherapy (HIPEC) technology was written into the Clinical Pathway of Radical Gastrectomy by the Ministry of Health in 2012 and it was used as a beneficial supplement for the postoperative treatment of gastric cancer. In the Amsterdam statement adopted at the 9th International Congress on Peritoneal Surface Malignancies in Netherlands in October 2014, HIPEC was considered as the recommended treatment for gastric cancer peritoneal carcinoma. Experts at the meeting highly praised the role of HIPEC in inhibiting the invasion and metastasis of gastric cancer. Our colleagues at home and abroad have been pursuing the accuracy and precision of hyperthermia. We also completed the research and development of precise intraperitoneal hyperthermia system earlier. The BR-TRG-I heat perfusion treatment system with full independent intellectual property rights has been developed and the technical method of "accurate, large capacity, continuous circulation" intraperitoneal heat perfusion chemotherapy has been established. Since 2012, the precise intraperitoneal hyperthermia chemotherapy system developed by the research group has achieved good therapeutic effect in tens of thousands of cases of gastric cancer in many large-scale hospitals in China, but the detailed mechanism has not been clear. Therefore, it is of great theoretical and clinical significance to elucidate the exact molecular mechanism of HIPEC and to explore a practical and effective treatment method to inhibit the progression of gastric cancer.

Materials and Methods

Cell, Main Reagents and Gastric Cancer Cell Line

BGC-823, MKN-28, MGC-803, SGC-7901, MKN-45 and GES-1 cell lines of normal human gastric mucosa were from the Cancer Hospital Affiliated of Guangzhou Medical University. They are all cultured in DMEM medium containing 10% fetal bovine serum in a constant temperature incubator of 37°C and 5% CO_2. Main reagents: DMEM culture medium was purchased from GIBCO; Trizol and Li-pofectamine 2000 was purchased from Invitrogen and real-time fluorescent quantitative PCR kit was purchased from Takara, Japan.

Expression of RP11-356I2.2 and Tumor Suppressor Gene KLF17 in Gastric Cancer Cell Lines and Tissues

The expression of RP11-356I2.2 and KLF17 in BGC-823, MKN-28, MGC-803, SGC-7901, MKN-45 cells, GES-1 cells and serum of patients with gastric cancer before and after HIPEC were detected by real-time quantitative PCR. Firstly, RNA was extracted from tissues and cells by Trizol method and then the total RNA was transformed into cDNA by reverse transcription kit. The relative expressions of RP11-356I2.2, KLF17 and internal reference GAPDH were detected by SYBR premix Ex Taq kit. Operate according to the instructions of the kit, the upstream primer of RP11-356I2.2 is 5'-CGCCTGGCTTATACCACC -3' and the downstream primer is 5'-TTCCCTCTCAGTCTCGCC-3'. The upstream primer sequence of KLF17 is 5'-GCTCACGCCTGTAATCCC-3' and the downstream primer sequence is 5'-TTCTCCCGTCAGTCTCCC-3'. The upstream primer of internal reference GAPDH is 5'-CCATGAGAAGTATGACAAC-3' and the downstream primer is 5'-GAGTCCTTCCACGATACC-3'. The relative expression of RP11-356I2.2 and KLF17 was expressed by $2-\Delta\Delta Ct$ method.

Disease-Free Survival (DFS) of Gastric Cancer Patients After HIPEC and Observation of Overall Survival (OS)

Follow-up of 60 patients with gastric cancer after CRS + HIPEC for 5 years, ① DFS refers to the time of recurrence or death due to disease progression after HIPEC treatment and ② OS refers to the time from the beginning of HIPEC treatment to the death caused by any reason.

Effect of Over-Expression of RP11-356I2.2 on KLF17 Expression

Western Blotting

The cells of the transfected group and the negative control group were collected and lysed with cell lysate. Take 20 μL l lysate for SDS-PAGE electrophoresis and transfer the expressed product to nitrocellulose membrane for reaction. Using glyceraldehydes phosphate dehydrogenises as a quantitative molecular mass marker (Maker), the hybridization images were analyzed by band scan 5.0 software.

The Expression of KLF17 Detected by Immunofluorescence

Take out the 12 hole cell culture plate in the super clean table, bake the cover glass that has been treated with sodium hydroxide and 75% alcohol in advance on the fire until it is dry and then put it into the 12

hole plate. Add 1 mL of cell culture medium containing 10% fetal bovine serum into each well, digest, disperse and inoculate the cells into 12 well plates, control the confluence at about 20% and culture. When the confluence of the cells reaches 40-50%, the cells are fixed. Take out the slide, drop the sealing solution containing DAPI dye, take out the cover slide in the 12 whole plates, screw it upside down on the sealing solution and observe under the fluorescence microscope.

Statistical Methods

Kaplan-Meier method was used to obtain the survival curve and log-rank method was used to analyze the statistical evaluation of survival rate. SPSS 19.0 software was used for data analysis. The measurement data were all expressed as mean ± standard deviation. The significant difference between the groups was analyzed by one-way ANOVA. The difference was compared by LSD analysis between the two groups. If the variance was not uniform, it was analyzed by Dunnett's method; $P<0.05$ means the difference was statistically significant.

Results

The Expression of RP11-356I2.2 Decreased in Gastric Cancer Cell Lines and Tissues

Through RT-PCR, it was found that the expression level of RP11-356I2.2 in most gastric cancer cell lines BGC-823, MKN-28, MGC-803, SGC-7901 and MKN-45 was significantly lower than that in GES-1, the difference was statistically significant ($P<0.05$), as shown in Fig. 1a. RT-PCR further detected that RP11-356I2.2 was low expression in gastric cancer and its expression level was inversely proportional to the malignant degree of gastric cancer, the difference was statistically significant ($P<0.05$), as shown in Fig. 1b.

After HIPEC, the Expression of RP11-356I2.2 and Tumor Suppressor Gene KLF17 Increased

RP11-356i2.2 and KLF17 expression were detected in the serum of gastric cancer patients before and after HIPEC. The results showed that the expression of RP11-356I2.2 and KLF17 was significantly increased after treatment compared with that before HIPEC in patients with gastric cancer ($P<0.05$) as shown in Fig. 2.
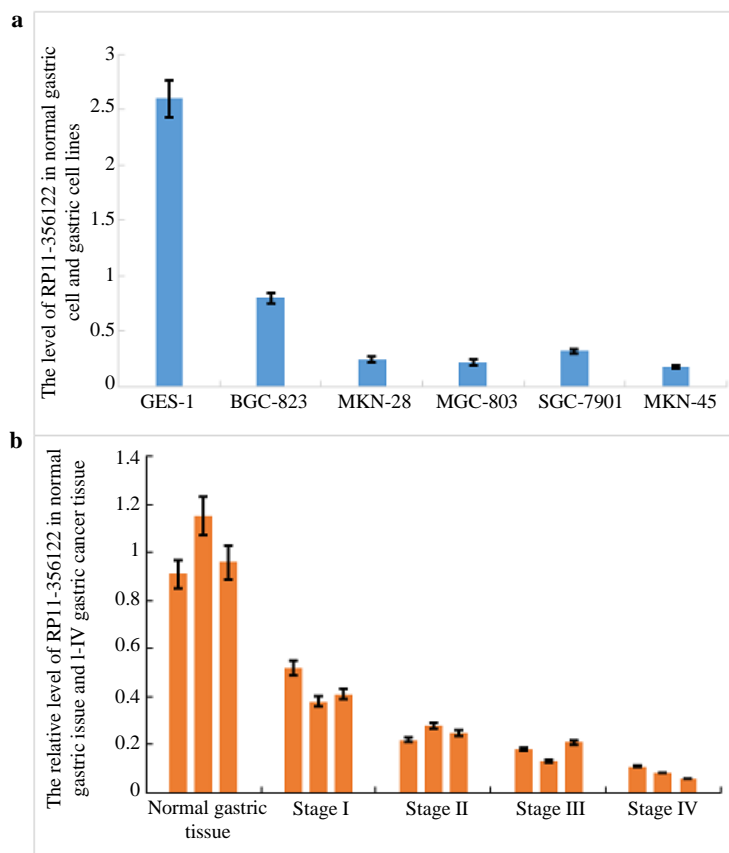

Fig. 1: Expression of RP11-356I2.2 in gastric cancer cell line and gastric cancer tissue; (a) Expression of RP11-356I2.2 in gastric cancer cell line (b) Expression of RP11-356I2.2 in gastric cancer tissue
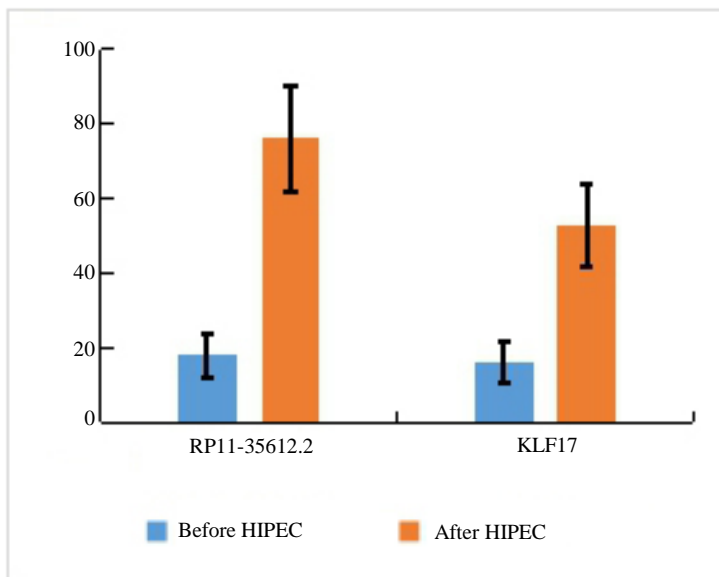
Fig. 2: Expression of RP11-356I2.2 and KLF17 in serum of gastric cancer patients before and after HIPEC
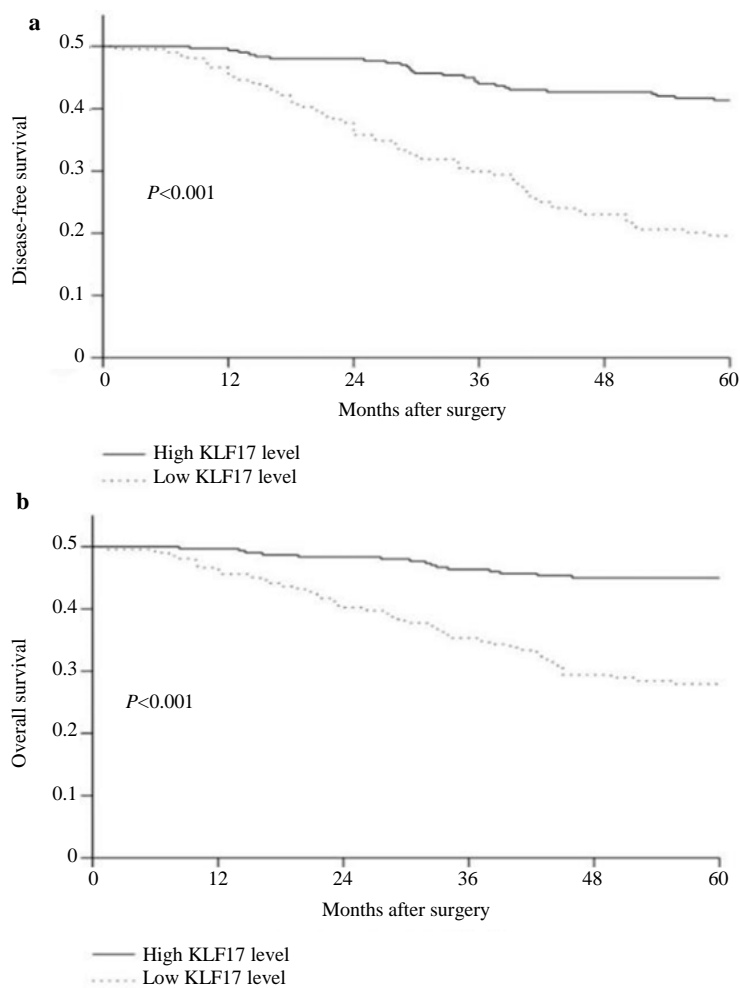

Fig. 3: Disease Free Survival (DFS) and Overall Survival (OS) after HIPEC in gastric cancer patients. (a) Progression Free Survival (DFS) after HIPEC in patients with gastric cancer (b)Total Survival rate (OS) of gastric cancer patients after HIPEC
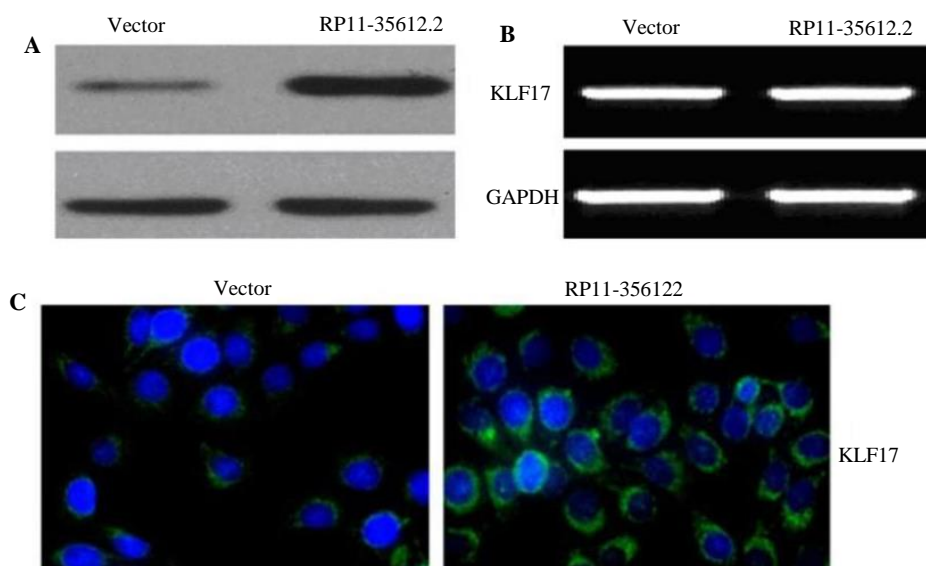
Fig. 4: Effect of RP11-356I2.2 on KLF17 of SGC-7901 cell. (a) Immunoblotting results (b) RT-PCR results (c) Immunofluorescence results

After HIPEC, the DFS and OS were High in KLF17 High Expression Group

Progression Free Survival (DFS) refers to the time from the beginning of HIPEC to the recurrence or death of gastric cancer. Overall Survival (OS) refers to the time from HIPEC to death (for any reason). We followed up 60 gastric cancer patients for 5 years. The DFS and OS of KLF17 high expression group were 9.7 and 14.2 months respectively, which was significantly longer ($P<0.05$) than those of KLF17 low expression group Fig. 3a (5.4 months) and OS Fig. 3b (10.2 months).

Effect of RP11-356I2.2 on KLF17 of SGC-7901 Cells

SGC-7901/RP11-356I2.2 cells were stably established. Western blotting Fig. 4a and immunofluorescence Fig. 4c showed that KLF17 protein was up-regulated and the difference was statistically significant ($P<0.05$). However, there was no significant difference in mRNA level and the difference results have no statistical meaning ($P>0.05$) as shown in Fig. 4b.

Discussion

The analysis of sequencing results of human genome shows that only a small part ($< 2\%$) of the whole genome can encode protein DNA and most of them are non-coding DNA. The products of these DNA transcriptions are non-coding RNA (ncRNA) (Qi and Du, 2012). Long non-coding RNA (LncRNA) refers to the non-coding RNA with a length of more than 200 nt, which is transcribed by RNA polymerase II (pol II). Its

biosynthesis is similar to that of mRNAs and it is an important member of mammalian transcription group that has attracted much attention in recent years (Gil and Ulitsky, 2019). As a kind of NC RNA, LncRNA does not encode protein or only encodes very short polypeptide, which is initially considered as "noise" of gene transcription and has not been paid attention (Calin *et al*., 2007; Wilusz *et al*., 2009). However, recent studies have shown that LncRNA is involved in many important signal transduction processes including genomic imprinting, chromatin modification, transcriptional activation, post transcriptional regulation and protein function regulation. It is widely involved in the process of tumor cell proliferation, apoptosis, differentiation, invasion, migration and angiogenesis and is closely related to the occurrence, development and prognosis of many tumors (Samata and Akhtar, 2018; Sherstyuk *et al*., 2017). Research showed that the expression level of some specific LncRNA in tumor cells will change and the LncRNA with this change can be used as a marker and potential drug target for cancer diagnosis (Lin and Yang, 2018; Guo *et al*., 2019). Recent studies have shown that LncRNA hotspots play an important role in the occurrence and development of many human malignant tumors. For example, LncRNALL22NC03-N64E9.1 controls the progression of lung cancer by regulating cell proliferation (Jing *et al*., 2018). LncRNAOIP5-AS1 promoted the migration and invasion of cervical cancer cells through miR-143-3p (Chen *et al*., 2018). Chen *et al*. (2016) that up-regulation of lncRNA HOTTIP can promote the metastasis of Esophageal Squalors Cell Carcinoma (ESCC) through EMT induction. These results indicated that a group of LncRNA have changed in the development of malignant

tumor and participate in the regulation of key signal transduction pathways. However, the clinical significance and potential mechanism of lncRNA hotspot in gastric cancer are not clear.

In the previous study, it was found that there are 33045 abnormal LncRNA were expressed by high-throughput LncRNA expression microarray. There were 566 cases with more than 2-fold up-regulation, of which RP11-356I2.2 was significantly up-regulated in the serum of 6 gastric cancer patients after HIPEC and it was more than 12 times up-regulated, which was verified by quantitative RT-PCR (Zeng *et al*., 2015). On this basis, we carried out this study to further study the biological function of RP11-356I2.2. Among lncRNAs, lncRNA RP11-356I2.2, a novel lncRNA, also known as LINC02539, located in human chromosome 6q23.3 that encodes a long intergenic noncoding RNA. Fagerberg *et al*. (2014) Analyzed the transcripts of 27 different organs and tissues from 95 individuals by RNA sequencing and found RP11-356I2.2. It was found that the expression of RP11-356I2.2 decreased in gastric cancer cell line: RT-PCR showed that the expression level of RP11-356I2.2 in most gastric cancer cell lines (BGC-823, MKN-28, MGC-803, SGC-7901 and MKN-45) was significantly lower than that of GES-1. At the same time, the detection of gastric cancer tissue showed that the expression was low in gastric cancer tissue and its expression level was inversely proportional to the malignant degree of gastric cancer. These results indicate that RP11-356I2.2 can be used as a biomarker for monitoring gastric cancer.

The family of Sp/KLF transcription factor has many biological functions. Their common point is that they all connect GC box and CACCC box sequence through a highly conserved DNA binding domain (Wolfe *et al*., 2000). According to the characteristics of the zinc finger DNA binding domain of the family, as one member of KLF family, KLF17 was identified by homology screening in mammalian EST database. In the mouse gene, this KLF17 homologue is also known as Zfp393. KLF17 has an open reading frame of 1170-nt and is predicted to encode 389 amino acids. The gene is located at 1p34.1. Recent studies show that KLF17 inhibits EMT and metastasis in NSCLC in a p53 dependent manner (Ali *et al*., 2015). In colorectal cancer, the expression of KLF17 decreased and the prognosis of patients with positive expression of KLF17 was better than before (Jiang *et al*., 2019). In esophageal cancer patients, KLF17 inhibited the proliferation, migration and invasion of esophageal cancer cells and was negatively correlated with lymph node metastasis of esophageal cancer (Li *et al*., 2015). In this study, 60 patients with gastric cancer after CRS+HIPEC were followed up for 5 years. It was found that PFS and OS in KLF17 high expression group were significantly longer than those in low expression group. At the same time, we established a cell model of over expression of RP11-

356I2.2. Western blotting Fig. 4a and immunofluorescence Fig. 4c confirmed that over expression of RP11-356I2.2 could cause up-regulation of KLF17 protein.

Conclusion

Traditional chemotherapy provides similar cytotoxic drug levels in normal and tumor tissues. Due to the significant dose limiting toxicity, the drug level in tumor tissues may not be able to effectively control the growth of cancer cells. Those Remaining Free Cancer Cells (FCC) were isolated by abdominal adhesions with relative lack of blood supply, which at least partially explains the reason why systemic treatment alone has little effect on local advanced gastric cancer (Stewart and Shen, 2005). Because the peritoneal-plasma barrier limits the therapeutic effect of intravenous administration and the direct administration of cytotoxic drugs can increase local exposure and reduce systemic toxicity. On the one hand, drugs enter the systemic circulation by dispersion or absorption from the peritoneum. On the other hand, the drug will also be absorbed into the portal vein blood by covering the liver, spleen, stomach, small intestine and large intestine as well as the peritoneal visceral layer on the surface of mesentery (Katz and Barone, 2003). This route provides treatment for potential liver micro metastasis. Because of the peritoneum blood barrier, the level of intraperitoneal chemotherapy drugs is 20 to 1000 times higher than that of plasma (Van der Speeten *et al*., 2012). HIPEC combines the inherent intracavitary delivery of certain cytotoxic drugs, resulting in regional dose intensification and pharmacokinetic advantages of direct cytotoxic effects of hyperthermia. Hyperthermia has been shown to selectively kill tumor cells by inhibiting DNA replication, transcription and repair of essential nuclear matrix (Roti Roti *et al*., 1998). It can also enhance the cytotoxic effect of some chemotherapy drugs and improve the tissue permeability of drugs (Sticca and Dach, 2003). Some studies have also shown that hyperthermia can enhance the immune attack on tumors (Frey *et al*., 2012). Studies have shown that postoperative hyperthermia can reduce local recurrence of brain metastases (Byun *et al*., 2018). HIPEC has traditionally been used for the treatment of peritoneal cancer and in combination with tumor Cell Reduction Surgery (CRS). CRS and HIPEC were initially used for the treatment of appendiceal cancer and malignant peritoneal mesothelioma (Sugarbaker *et al*., 1990; Sugarbaker, 2016; Feldman *et al*., 2003).

To sum up, this study confirmed that the up regulation of klf17 protein by rp11-356i2.2 may be one of the mechanisms of HIPEC inhibiting the development of gastric cancer, providing reference basis and ideas for rp11-356i2.2 as a new target of inhibiting the metastasis of gastric cancer cells. Therefore, it is necessary and valuable to further research the mechanisms of how

RP11-356I2.2 regulated KLF17 and make RP11-356I2.2 transform a clinical marker.

Author's Contributions

Yu Yan, Feng Yanlin and Zhang Xiangliang: Designed and performed the experiments, analyzed the data and prepared the paper. Both authors contributed equally to this work.

Feng Jinxin and and Li Kejun: Participated to collect the materials related to the experiment.

Liu Gaojie: Designed the experiments and revised the manuscript.

Conflict of Interest

The authors declare that they have no competing interests. The corresponding author affirms that all of the authors have read and approved the manuscript.

Ethics

The authors declare their responsibility for any ethical issues that may arise after the publication of this manuscript.

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