RNA interference in the progress of gastric cancer

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Abstract: Gastric cancer is one of common malignant tumors. The development of molecular biology and genetics prompts people to regulate tumor cell regulation from the gene level, and seeks method to the new tumor therapy. RNA interference (which is also called RNAi) is a technology of double stranded RNA exogenous or dsRNA into cells, therefore this thereby inhibits the expression function of corresponding target gene. This paper summarizes the development process and the mechanism of RNAi technology, outlines the progress of experimental gastric cancer of the current RNAi technology, which shows that this technology can directly or indirectly inhibit tumor, and reduce the drug resistance of tumor cells. With the gradual improvement of RNAi technology, it will become a new direction for gene therapy of gastric cancer.

Keywords: Gastric cancer, RNAi, gene therapy, inhibiting effect.

INTRODUCTION

Gastric cancer is one of the most common malignant tumors, according to the relevant statistical data in 2000 to cancer 2 cause of death in gastric cancer mortality worldwide, and is a high incidence of gastric cancer in China accounted for 42% of the world's number of gastric cancer, mortality in the first (Xu and Wang, 2006) to malignant tumor. With gastroscope, laparoscopic and barium meal examination mode in basic-level hospitals widespread popularization, to improve the detection rate of a certain degree of gastric cancer. Although we has used the comprehensive treatment measures such as surgery, chemotherapy and radiotherapy to treat, but for advanced gastric cancer patients, due to the low resection rate, side effects, and drug resistance, the cure effect is not ideal. With the development of molecular biology and medical genetics, controlling tumor related genes from gene level is a new thought for gastric cancer therapy. RNA interference (RNAi) technology is the development of a new technology in recent years, will be sent to you by exogenous or endogenous double-stranded RNA (dsRNA) double stranded RNA, into the cells, leading to dsRNA homologous and the degradation of specific mRNA happen, thereby inhibiting the expression of target genes corresponding role. The method is efficient, fast, specific and stable to curb excessive expression of cancer related genes, and thus become a hot spot in the study of tumor gene therapy. In this paper, the research progress of RNAi technology in gastric cancer gene therapy were reviewed.

SUMMARY OF RNAi

The development history of RNAi

In 1990, JORGENSEN, etc will be purple pigment synthetase genes into petunias, the results did not make color deepened, as expected, instead of the noise and white or purple genes have been silent for (Jorgensen, 1990). In 1995, GUO and KEMPHUES in beautiful new elegans par - 1 gene antisense RNA RNA accidentally discovered that justice can also inhibit the expression of the gene, the result is as convoluted (Guo and Kemphues, 1995) at that time. Found in 1998, the FIRE on c. elegans research, injection of double-stranded RNA purification to nematodes after its gene inhibition effect is significantly higher than that of single-stranded RNA (antisense RNA or RNA) justice gene inhibition effect, they say the specific gene silencing phenomenon caused by the dsRNA as RNAi (RNA interference) (Andrew *et al.*, 1998). The discovery caused a large number of membrane biological for use RNAi to knockout research, which found in fruit flies, insects, plants, polyps, zebrafish, and other eukaryotes have the phenomenon occurred. Because of double-stranded RNA in mammalian cells there are nonspecific physiological role, and therefore there is no found effective RNAi in mammals effect. Elbashir in 2001, the synthesis of 21 nt - dsRNA into mammalian cells, the cells presented effective RNA interference effect, the application of RNAi in higher animals provides may (Elbashir *et al.*, 2001). Initially compound RNAi double-stranded RNA interference technique can only transient transfection, in 2002, contains Brummelkamp etc to build the H1 promoter in mice small hairpin RNA (small hairpin RNA, shRNA) expression vector, and in mammalian cells effectively reduced the expression of target genes, which laid the groundwork for RNAi technology to further expand the application (Brummelkamp *et al.*, 2002). RNAi technology for the development of gene therapy, antiviral drugs research and development, and explore the gene function research provides a new way, and quickly

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become a research hotspot. In 2001 and 2002 by Science magazine rated as one of the top ten scientific achievements, and won the Nobel Prize in 2006.

The mechanism of RNAi

At present it is generally believed that the mechanism of action of RNAi consists of two phases (fig. 1) (Tomari and Zamore, 2005).

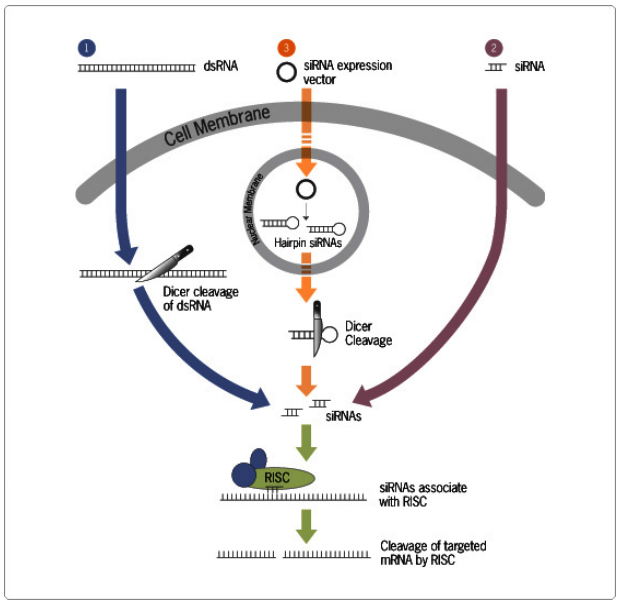

Fig. 1: Preparation for different extraction components of Pu'er Tea.

(1) start-up stage: through exogenous genes into, transposon transcription and RNA virus infection to dsRNA enter cells, cytoplasm of endonuclease Dicer (Rnase β one of the family, can specific cutting dsRNA endonuclease) to identify and cut dsRNA, dsRNA cutting into 21~23 bp (base pairs) of double chain small interfering RNA (small interfering RNA, siRNA), each siRNA3 'side contains two bases (Hutvagner and Zamore, 2002) and 5' terminal phosphate (Zamore *et al.*, 2000). Stage (2) effect: intracellular RNA helicase siRNA solution chain into chains, antisense strand and justice which antisense siRNA and some enzymes in the body, such as the helicase, circumscribed enzyme, enzyme etc, combining to form compounds induced characterized by RNA silence (RNA - induced silencing complex, RISC) (Hammond *et al.*, 2000). SiRNA can guide RISC and corresponding the mRNA sequence homologous region specificity, RISC can cut mRNA in combination with parts (Meister *et al.*, 2004), about the parts in siRNA 12 base (Lipardi *et al.*, 2001), the 3 'end of the cut after fracture mRNA further degradation will happen immediately, so as to induce the host cell against these mRNA degradation reaction. SiRNA of homologous single mRNA in guiding RISC cutting at the same time, also can be used as a primer combination target RNA, the RNA polymerase (RdRP) RNA - dependent RNA polymerase, under the action of synthesize more new dsRNA, newly synthesized dsRNA again by endonuclease cutting Dicer, thus forming the amplification effect of RNAi, produce a large number of subprime siRNA, eventually will the effect of the target mRNA degradation completely (Dykxhoorn *et al.*, 2005).

The characteristics of RNAi

RNAi technology since found have been the attention of scientists, has been widely used and rapidly, it is inseparable with its unique characteristics, its main characteristics are the following: (1) high efficiency: through the catalytic mechanism of amplification, can be achieved under the effect of trace amounts of dsRNA, effectively inhibit the expression of target genes for, even to knockout (if you out). (2) highly specific: siRNA antisense strand will only target mRNA and homologous region specificity, therefore has a strict sequence specificity and has nothing to do with sequence expression did not interfere with function, can be used in the inhibition of a single nucleotide mutation gene expression (Xia *et al.*, 2004). (3) can be transmitted and heritability: after lots of siRNA in cell amplification can be transport out of the cell, which is passed between different cells. Song E etc. Research shows that when rats after tail vein injection of siRNA targeting Fas gene in liver cells also appeared the same RNA molecule (Song *et al.*, 2003). In c. elegans, the study found the gonads to inject dsRNA can result in offspring inhibition gene in 4, effect of RNAi can be genetic. (4) inhibition rapidly: dsRNA into the cell, can rapid degradation of homologous mRNA in the cytoplasm, the study found that 30 min can make mRNA expression levels fall by 30 times (Yang *et al.*, 2000). (5) strong stability: siRNA can stable in 3-4 d within the cell, the half-life is far higher than that of antisense RNA. (6) has a length dependency, ATP dependent, simple operation and other characteristics.

Application of rnai in gastric cancer therapy

RNAi role in gastric cancer related gene research

The occurrence of gastric cancer is a complicated process, it is integrated in a variety of genetic and environmental factors, through the activation of oncogenes and the inactivation of tumor suppressor genes, resulting in a multi-stage, multi- step process, eventually leading to the malignant cell proliferation and apoptosis. RNAi can be deliberately aimed at target genes, by blocking the activation of oncogenes and the inactivation of tumor suppressor genes, achieve the goal of treatment of gastric cancer. Compared with the past method of gene therapy, RNAi can mutual interference of multiple target genes inhibited at the same time, achieve the goal of inhibiting tumor development. Since RNAi technology found, because of its unique advantages, has been widely studied in tumor gene therapy.

Jinawath N (Natini *et al.*, 2004) design such as the specific siRNA targeted protein NOL8 nucleoli, transfection, MNK45, ST to TMK-1-4 three different diffuse gastric cancer cells, the discovery can significantly reduce the expression of the gene, and cause cells to apoptosis. The Bcl - 2 is a play a role in regulation of cell apoptosis genes, and its expression and the occurrence of gastric carcinoma has close relations, Hao JH, (Hao *et al.*, 2007) by siRNA transfection SGC790 gastric cancer cells, found that the expression of Bcl-2, slowing the growth of gastric cancer cells, inhibition of telomerase activity. Survivin cells (survivin) is a widely expressed in many cancer cell apoptosis inhibition factor, it in the inhibition of apoptosis and regulation play a role in cell division. Miao, etc. (Miao *et al.*, 2007), the study found the specificity of targeting survivin gene RNAi can realize mRNA and protein expression of survivin inhibition effect, cause apoptosis and inhibit tumor growth. P38 lightning is PLK-1-an important protein in MAPK signal pathway, regulation by various factors, Lan etc. (Lan *et al.*, 2006) use of RNAi, siRNA compared with control group, the transfection group of PLK-1 expression in gastric cancer cell lines MKN45 significantly reduced, slow in cell proliferation, apoptosis levels. P42.3 is a specific expression genes in gastric cancer tissue, which were not expressed in normal gastric mucosa tissues, and in early gastric cancer tissue increased, the role is not clear in the signal path. By RNAi technology found that p42.3 by regulating the expression of cell cycle protein B1 and Chk2, caused by excessive proliferation, cell produce tumorigenic (Fan *et al.*, 2007). Over expression of heat shock protein (HSP) 70 can cause stomach performance and maintain the malignant transformation, such as Xiang (Xiang *et al.*, 2008) using RNAi technology for gastric cancer cell line BGC823 of HSP70 on targeted interference, results show that the proportion of S stage cells is reduced, the stagnation of the cell cycle, cell apoptosis increases. ID1 (inhibitor of DNA binging/differentiation 1) is the factor of multiple signaling pathways regulating the activation energy increased VEGF expression, and promote the proliferation of tumor cells. Lei, etc. (Lei *et al.*, 2007) through the ID1 specific siRNA RNAi, according to the results of ID1 mRNA and protein expression decreased, nude mice group interference tests showed that the tumor weight lower than experimental group. This proves the ID1 can promote the proliferation of tumor. With the discovery of the new oncogene and tumor suppressor genes, to various factors, a deeper understanding of the interactions between the occurrence and proliferation of gastric cancer, further understanding, RNAi technology will has a bright prospect in gastric cancer gene therapy.

RNAi indirectly through inhibiting tumor blood vessels and lymphatic hyperplasia treatment of gastric cancer

Division of tumor cells, tumor growth and metastasis depend on angiogenesis, so inhibit the angiogenesis can disease for the treatment of malignant tumor, etc. Vascular endothelial growth factor (VEGF) in quite a few strongest role in promoting angiogenesis factor, in every link of tumor angiogenesis play an important role and can be specifically ACTS on endothelial cell mitogen, therefore targets VEGF targeted by RNAi technology can effectively inhibit tumor angiogenesis, to effectively inhibit tumor growth. Xu etc. (Xu *et al.*, 2006) using RNAi technology, designs two groups of siRNA targeting VEGF transfection SGC7901 gastric cancer after VEGF mRNA transcription and protein expression in cells, the cell cycle change and S phase cells decreased, cell value, be suppressed. Xue, etc. (Xue *et al.*, 2004) will be targeted at Racl siRNA expression vector transfection AGS gastric cancer cell line, found can effectively suppress the expression of Racl, promote cell apoptosis, also found that cells in the tumor suppressor gene p53 and angiogenesis inhibiting factor expression of VHL rise, while VEFG and hypoxia induced factor (hypoxia-inducible factor, HIF) -l alpha expression, which indicates that Racl in tumor cells can regulate a correlation factor of angiogenesis, promoting the generation of blood vessels. Meng etc. (Fanping *et al.*, 2005) using SGC7901 gastric cancer cells, the study found by RNAi gene silence Raf - 1, VEGF and hypoxia induced factor-l alpha expression, namely the inhibition of angiogenesis and promote the apoptosis of gastric cancer cells. Lei, etc. (Lei *et al.*, 2007) using RNAi SGC7901 gastric cancer with high expression of cox-2 silence, found that transfection cox-2 siRNA experimental cell differentiation inhibitory factor 1 (Id-1) and the expression of VEGF decreased, which showed that the Id-1 in the process of cox-2 mediated angiogenesis play a role, has the potential to be a new gene therapeutic targets.

Lymphatic generated for the transfer of tumor cells play a facilitating role. VEGF - C in stimulating growth of lymphatic endothelial cells and lymphatic vessel formation plays an important role, so in gastric cancer and other malignant invasive tumors in the high expression of VEGF - C can cause the lymph node metastasis of tumor. Zhou Huicong (Huicong *et al.*, 2007), etc. By building the siRNA targeting VEGF - C expression vector transfection gastric cancer cell line SGC-7901 display can significantly nhibit VEGF - C protein expression, He (He *et al.*, 2008), such as use of new nano materials as transfection carrier, the VEGF-C siRNSA SCG7901 import cancer of the stomach, realized with VEGF - C gene silencing, the result shows that the tumor lymphatic generated, be suppressed, reducing tumor growth and invasion ability.

RNAi study of gastric cancer drug resistance

Chemotherapy is one of the main means of treatment of gastric cancer, and the drug resistance of tumor cells are often the main cause of chemotherapy failure. Molecular structure of its resistance to a variety of different,

different targets, mechanism of action of drugs multi-resistant (multi - drug to hold, MDR). The drug resistance of tumor is caused by some resistance genes, RNAi can be specifically targeted certain resistance related gene, gene silencing, to improve the effect of chemotherapy. Multi-drug resistance caused by the main resistance gene is more resistant gene 1 (MDR1) and its coding is a transmembrane glycoprotein of molecular weight of 170000 P-gp (P-glucoprotein) (*T*homas and Coley, 2003), this protein has the drug pump, when its abnormal expression or function within the cell, will be in the form of energy will be converted to antitumor drugs from cells, reduce intracellular drug concentration, the inhibition of Caspases apoptosis pathway at the same time, the cells become resistant (Rittierodt and Harada, 2003). Stege A (Stege *et al.*, 2004) in RDB EPG85-257 gastric cancer cells, using RNAi technology to MDR1 cell in silence, the mRNA and protein expression inhibition rate reached 91%, and the cells of tumor drug soft erythromycin resistance are reduced by 58%, the result shows that RNAi in inhibiting tumor cell resistance has A good application prospect.

ZNRD1 is P-gp transcription related genes, and the cut could cause the MDR1 expression transcription activity. Hong etc. (Hong *et al.*, 2004) targeted ZNRD1 siRNA carrier is designed. Transfection into gastric cancer SGC - 7901, reduces the expression of ZNRD1, and cells of doxorubicin, vincristine, ghost mortar increased b fork glucoside of drug sensitivity. Tumor susceptibility gene (tumor suscepitibility 101, gene TSG101) is a more resistant gastric cancer high expression of genes, and their function is associated with transcriptional regulation. Shen, etc. (Xia *et al.*, 2004) use vincristine resistance of gastric cancer SGC-7901 cells, using RNAi gene TSG101 silence, according to the expression of TSG101 significantly decreased, cell of TSG101 sensitivity at the same time, it shows that TSG101 play an important role in drug resistance in gastric cancer cells. MDR1 expression of the need to stimulate the activation of transcription factors, and CtBP1 (C - teminal - binging protein 1) in multi-drug resistance of cancer cells with high expression of a transcription factor. Jin etc. (Jin *et al.*, 2007) using RNAi CtBP1 expression suppression, of MDR1 mRNA and P-gp expression decreased. If the CtBP1 expression vector transfection with MDR1 promoter in gastric cancer cells and MDR1 promoter activity decreased obviously. Illustrate CtBP1 in MDR1 transcription activation. Hao etc. (Hao *et al.*, 2007) use of RNAi blockage cytokines induced apoptosis in gastric cancer-1 (cytikine-induced apoptosis inhibitor 1, CIAPIN1) conducted interference, found the MDR 1 and MRP-1 expression decreased, cell resistance decreases. Telomere repeat sequences factor 2 (telomeric repeat binging faceor 2, TRF2) is a kind of DNA damage in cells factor, the study found that the resistance of adriamycin and etoposide high expression of gastric cancer SGC - 7901 cells, such as Hanbing (Hanbing *et al.*, 2006) use RNAi to interference, TRF2 cell resistance decreases, suggests TRF2 resistance related to gastric cancer cells.

Problems and prospect

RNAi technology, much attention has been paid to discovered the method improving route, has been gradually behavior of a set of mature molecular biology methods. But really are widely used in clinic, there are many questions need us solve. For example when we import siRNA in the human body will bring unpredictable harm, whether applied results in human body and *in vitro* experiments and animal model of experimental results is consistent, whether there is a difference between different individuals. The technology application in the human body at the same time there is stability of siRNA and lack of efficient and low toxicity for human body transport carrier, etc. As the further understanding of RNAi mechanism, these problems could be solved, the application will be further promote (Kim and Rossi, 2007).

The occurrence of gastric cancer is a variety of carcinogenic factors and tumor-suppressor gene as a result, under the action of using RNAi technology for these key factors interference, reduce its expression, can inhibit tumor cell proliferation, invasion and drug resistance, achieve the goal of treatment of tumor. RNAi has been used to study the occurrence of gastric cancer development, aspects and so on for stomach cancer tumor vaccine and broad space. With the constant improvement of RNAi technology, it will become a new direction of the gastric cancer gene therapy.

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