Molecule action mechanisms of NM-3 on human gastric cancer SGC-7901 cells in vivo or in vitro

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INTRODUCTION
Apoptosis plays a key role in the proliferation and turnover of malignant tumor cells. It has been known that its extent is often enhanced in gastric cancer by some anti-cancer drugs, such as chemotherapeutic drugs, hormones or immune agents, microvascular growth inhibitors have been proved to have some inhibitory effects on malignant tumors, especially on gastric tumors. But it has not been clear whether NM-3 is a microvascular inhibitory agent for solid tumor growth. It might suppress gastric cancer cell proliferation and cause tumor cell loss and nuclear condensation in vitro. Up to date, NM-3 is considered as the newest micro-vascular inhibitor. Combined with carboplatin, it can soften hard lumps and dissolve phlegm, enhance apoposis of human gastric cancer xenografts in nude mice. On the other hand, NM-3 can enhance the sensitivity of chemotherapeutic drugs on human gastric cancer. Based on previous studies, NM-3 exerts its effects on solid tumor growth by promoting apoposis of human gastric cancer cell SGC-7901 and increasing the suppressive effects of carboplatin.

MATERIALS AND METHODS
Materials
A human gastric cancer cell line SGC-7901 grafted onto nude mice was used as the animal model, the age of these 60 mice was 6-7 weeks old female balb/c-nu/nu mice (weight 18-22 g) and a human gastric cancer cell line SGC-7901 was obtained from Shanghai Tumor Institute (No: 01842). The animals were subcutaneously xenografted under abdominal skin with the SGC-7901 cell line. The tumor transplantation procedure was described previously. The animal model and SGC-7901 cell line were obtained from Shanghai Experimental Animal Centre, Chinese Academy of Sciences.

NM-3 was composed of 2-chydroxy-6-methoxy-1-oxo-1-h-2-benzopyran-3-yd, concentration of NM-3 was 100 mg L⁻¹, the concentration of carboplatin was 100 mg L⁻¹.

Methods
Experimental schedule: After grafting, these nude mice were randomly divided into 3 groups: control group and two experimental groups assigned to receive NM-3 or carboplatin respectively. Each experimental mouse in two experimental groups was given a 0.5 ml dose of NM-3 drug via intra-abdominal injection or gastric perfusion (empty control group) once every three days over a 40-day period beginning at 1st day after being xenografted. The control animals received normal saline according to the same schedule by gastric perfusion. The animals were killed 41 days after being xenografted.

In our study, NM-3 induced gastric cancer cell apoptosis, and enhanced the chemotherapeutic sensitivity of human gastric cancer cell line SGC-7901 on carboplatin in vitro. Apoptosis induced by NM-3 needed further investigation.

Therapeutic effects on human gastric cancer cell growth were assessed. Tumor size was measured twice a week by multiplying two perpendicular diameter and tumor weight was determined immediately by electron balance after the animals were killed. Apoptotic cells and apoptotic index were assessed. Tumor size was measured twice a week by multiplying two perpendicular diameters and tumor weight was determined immediately by electron balance after the animals were killed.
determined by the terminal deoxynucleotidyl transferase-mediated deoxy-uridine triphosphate-fluorescence nick end labeling (TUNEL) method and flow cytometry analysis. Morphological alterations were observed with electron microscope.

Flow cytometry analysis: Propidium iodide (PI) staining was used for flow cytometric detection of apoptosis. 1x10^6 cells from each of the samples were treated with RNase and stained with PI. The apoptotic cells labeled by DNA strand were measured with a flow cytometer (FACS Calibur, Becton Dickinson, U.S.A.). The data from 1x10^6 cells/sample were collected, stored, and analyzed using CELLQUEST™ T and MODFITLT for macV1.01 software[4-12].

Statistical analysis
The results were expressed as ±s. Student’s t test was used. P value <0.05 was considered significantly.

RESULTS
NM-3 inhibited growth of micro-vascular of tumor in nude mice with human gastric cancer SGC-7901
NM-3 group decreased significantly the neo-microvascular density (1.17±0.05 mm²) of gastric cancer tumor implanted onto nude mice was significantly decreased in NM-3 group compared with that in saline group (5.37±1.12 mm²) and carboplatin group (4.72±1.18 mm², P<0.05). The microvascular density in NM-3 combined with carboplatin group (1.18±0.05 mm²) was not significantly different from that in NM-3 group (P>0.05, Table 1).

Table 1 Growth of neo-microvascular around gastric tumor supressed by NM-3 (±s)

| Treatment             | n | Density (mm²) |
|-----------------------|---|---------------|
| Carboptin             | 10| 4.72±1.18     |
| NM-3 plus carboplatin | 10| 1.18±0.05     |
| Saline                | 10| 5.37±1.72     |

P>0.05, P<0.01 vs t test in saline control group.

NM-3 enhanced sensitivity of carboplatin on human gastric cancer cell line SGC-7901 in vitro or in vivo
The apoptotic index (AI) of SGC-7901 induced by carboplatin was enhanced in NM-3 group. The apoptotic index (TUNEL: 27.98±6.12 %, FACScan: 26.86±5.69 %) was markedly increased in that of carboplatin group by using either TUNEL method or flow cytometry analysis compared with the carboplatin group (TUNEL: 12.94±2.12 %, P<0.01; FACScan: 11.86±1.09 %, P<0.01). The apoptotic index in NM-3 group (TUNEL: 16.47±4.13 % FACScan: 15.97±1.49 %) was higher than that in normal saline group (TUNEL 1.83±0.12 %, P<0.01; FACScan: 1.06±0.09 %, P<0.01, Table 2).

Table 2 Apoptotic index (AI) of human gastric cancer cell line SGC-7901 enhanced by NM-3 in vitro (±s)

| Treatment             | n | AI (TUNEL) % | AI (FACScan) % |
|-----------------------|---|--------------|----------------|
| NM-3                  | 10| 16.47±4.12   | 15.97±2.49     |
| Carboptin             | 10| 12.94±2.12   | 11.86±1.09     |
| NM-3 plus carboplatin | 10| 27.98±6.12   | 26.86±5.69     |
| Saline                | 10| 1.83±0.12    | 1.06±0.09      |

P>0.05, P<0.01 vs t test, in saline control group.

DISCUSSION
Gastric cancer remains one of the most common causes of cancer-related death in the world. At present, gastric cancer is still diagnosed at its advanced stage in most patients throughout the world. Even with curative resection, they remain at a high risk of relapse[13-32]. Thus, there is a great need for effective adjuvant therapy for patients with gastric cancer. Our previous clinic paired comparative studies suggested that NM-3 had therapeutic effects on advanced gastric cancer. It could increase the surviving period of the patients, improve the life quality and increase the metastasis and recurrence after operation because of its lower toxic side-effect compared with intravenous chemical therapy[33-47]. Up to date, the effect of NM-3 on human gastric cancer has not been reported in the world. So we thought it is worth to make a further research on its anti-cancer mechanisms.

Gastric cancer is not only a disease with abnormal cell proliferation and differentiation, but also a disease with abnormal apoptosis. Enhanced apoptosis in human gastric cancer cells could be observed after treatment with 5-fluorouracil, cisplatin, arsenous oxide, etc. These data suggest that it is a therapeutic method for patients with gastric cancer to induce apoptosis of cancer cells[41]. The present study indicated that tumor growth was significantly inhibited by treatment with carboplatin or NM-3. The results obtained by TUNEL method and cytometry analysis suggested that gastric cancer cells were suppressed in vivo, NM-3 was related to the induction of apoptosis of human gastric cancer cell line SGC-7901. These data suggest that NM-3 can inhibit gastric cell proliferation. So inhibition of gastric cancer induced by NM-3 is also related to the suppression of its proliferation.

Apoptosis is a complex and active cellular process, whereby individual cells are triggered to undergo self-destruction in a manner that would neither injures neighboring cells nor elicits any inflammatory reaction. Various triggering factors initiate corresponding proteo-lysis cascade reaction depending on mitochondrion or APO 1/FASCD95 receptors mediate apoptotic pathways. There are oncogenes and tumor suppressor gene products in the regulation and execution of apoptosis.
It has been proved that p53, Rb, myc, ras, raf, play important roles in apoptosis and are thus named the guardians of genomes. They monitor the state of DNA and cell cycle is blocked in case of DNA damage. This takes place through the induction of CIP/Swaf/p21. In the absence of phosphorylated active cyclin-dependent kinases, the cell cycle remains inactive (unphosphorylated). This leads to activation of DNA repair machinery. If DNA repair fails, p53 will take over again and trigger apoptosis in a process that involves upregulation of the apoptosis-inducing bax and down-regulation of the apoptotic bal.

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