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ZNF217 expression correlates with the biological behavior of human ovarian cancer cells*

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Abstract ***Objective:*** The aim of the study was to investigate the correlation of zinc-finger protein 217 (ZNF217) gene expression with the biological behavior of human ovarian cancer HO-8910 cells. ***Methods:*** The expression of ZNF217 in ovarian carcinoma cell lines was detected by RT-PCR and Western blot, respectively. The biological behaviors of the transfectants were investigated by MTT, *in vitro* Boyden chamber and *in vivo* invasion assay, respectively. ***Results:*** RT-PCR and Western blotting revealed that transfection of ZNF217 into the HO-8910 cells significantly increased their proliferation along with markedly enhanced *in vitro* and *in vivo* invasion and metastatic abilities. MTT assay showed that the proliferation ability of pEGFP-N1-ZNF217/HO-8910 cells was significantly higher than that of pEGFP-N1/HO-8910 cells and HO-8910 cells ($P < 0.001$). The Boyden chamber assay showed that the numbers of migrating pEGFP-N1-ZNF217/HO-8910, pEGFP-N1/ HO-8910 and HO-8910 cells were (141.25 ± 13.91) cells /200 × field, (82.50 ± 11.73) cells /200 × field and (81.75 ± 12.12) cells /200 × field, respectively, with a significant difference between them ($F = 29.274$, $P < 0.001$). The nude mouse experiment showed that the *in vivo* tumor formation ability of pEGFP-N1-ZNF217/HO-8910 cells was significantly higher than that of pEGFP-N1/HO-8910 cells ($P < 0.001$). ***Conclusion:*** Based on these clinical and laboratory observations, we conclude that ZNF217 may contribute to ovarian cancer invasion and metastasis, and associated with worse clinical outcomes. We evaluated ZNF217's role as a biomarker of ovarian carcinogenesis and tumor progression in patient samples and explored possible molecular mechanisms in promoting tumor growth and invasion.

Key words ovarian cancer; zinc-finger protein 217 (ZNF217) gene; gene expression; proliferation; invasion; tumor metastasis

Ovarian epithelial carcinoma is one of the most lethal gynecological malignancies found in humans. Exploring factors associated with ovarian cancer metastasis, and screening for specific genes to clarify the molecular mechanism of ovarian cancer metastasis, will provide the ideal target for the treatment of ovarian cancer. Our preliminary results showed that the zinc-finger protein 217 (ZNF217) gene expression is associated with ovarian cancer stage and differentiation [1]. In our study, we used the reverse transcriptase polymerase chain reaction (RT-PCR) to detect the expression of ZNF217 gene in ovarian cancer cell lines, and preliminary discussed ZNF217 genetic role in the invasion and metastasis of ovarian cancer with the methods of gene transfection and invasion and metastasis of cancer cells *in vitro*. The results reported as follows.

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Materials and methods

Materials

Human ovarian serous cystadenocarcinoma epithelial cells HO-8910 maintained by Department of Obstetrics of Nafang Hospital Research Labs (China). Trizol and Lipofectamine™ 2000 were purchased from Invitrogen, USA. DNase I from Sangon Biotech, Shanghai, China. Reverse transcription System from Promega, USA. ZNF217 and GAPDH primers designed with Primer 5.0 software, and synthesized by SBS Genetech, Beijing, China. ECoR I and RT-PCR kit purchased from TaKaRa, Dalian, China. Methyl thiazolyl tetrazolium (MTT) and G418 from Sigma, USA. ZNF217 polyclonal antibody from Abcam, UK. β-actin monoclonal antibodies from SantaCruz, USA. Boyden Transwell from Chemicon, USA. pEGFP-N1 plasmid from Dr. Jun Zhou, Southern Medical University, China. pEGFP-N1-ZNF217 plasmid built by Department of Obstetrics of Nafang Hospital Research Labs, China.

SPF nude mice (46 weeks) from Animal Center of Southern Medical University, China.

Experimental methods

Cell culture

Human ovarian serous cystadenocarcinoma epithelial cells HO-8910 were cultured in RPMI-1640 medium supplemented with 1% penicillin/streptomycin and 10% FBS. Cells were incubated at 37 ℃ in a humidified 5% CO_2 incubator.

Plasmid transfection and screening

HO-8910 cells were seeded to 24 well palates 1×10^5 cells per well one day before transfection, to make the cell fusion reached 90%–95%. Diluted the pEGFP-N1-ZNF217 plasmid DNA with 50 μL serum-free culture medium. Diluted 2 μL lipofectamine™ 2000 with 50 μL serum-free culture medium, incubated for 5 min at room temperature. And then mixed them into 100 μL, incubated for 20 min at room temperature. The 100 μL mixture was added to 24 well plates, and the liquid was changed after 6 h. Culture medium containing G418 (1000 μg/mL) was added after 48 h at 37 ℃ for resistance screening. Three weeks later, we chosen the strongest expression of the monoclonal cell fluorescence (Fig. 1) to expand training, and used for subsequent experiment. HO-8910 cells transfected with pEGFP-N1 plasmid were used as negative control, HO-8910 cells with no transfection as blank control.

RT-PCR to detect the expression of ZNF217 mRNA

Procedure was according to the instructions of reverse transcription kit. The upstream primer sequences of ZNF217 gene was 5'-AAGTATTGACCCTCTATGAT-3', and the downstream primer sequences was 5'-TATGTCCACAGTTCACCC-3'. The length of the product was 476 bp. Taken reduced glyceraldehyde-phosphate dehydrogenase (GAPDH) as an internal control, which upstream primer sequences was 5'-CACATCGCTCAGACACCA-3', and the downstream primer sequences was 5'-GGATCCCACGACGTACTCA-3'. Its product was 311 bp. The two pairs primers were in the same reaction system for PCR amplification, what was carried out as follows: a one-time denaturation for 5 min at 94 ℃; 30 cycles of 30-sec denaturation at 94 ℃, annealing at 58 ℃ for 30 sec, and extension at 72 ℃ for 30-sec, followed by a 5-min final extension at 72 ℃. PCR products were analyzed by 1% agarose gel electrophoresis, and the gray of stripe were analyzed by 1-DADWANCED software.

Western blot analysis to detect the expression of ZNF217 protein

The 30 μg protein of each group was extracted from pEGFP-N1-ZNF217/HO-8910, pEGFP-N1/HO-89l0 and HO-8910 cells. Diluted protein sample with 2 × protein electrophoresis buffer, and then transferred to ice after boiled 10 min at 100 ℃. To analyze ZNF217, proteins were separated on SDS-PAGE gels (60 V on laminated rubber 40 min, 100 V on separation rubber 180 min) followed by transfer onto polyvinylidene fluoride membranes with Bio-Rad miniature electric transfer system for 2 h. After blocking for 90 min with TBST, washed with TBST 4 times × 5 min, blots were probed at room temperature with goat anti-human polyclonal antibody to ZNF217 at a 1:200 dilution for whole night. After extensive washing with TBST (4 times × 5 min), the immune complexes were detected with horseradish peroxidase conjugated goat anti-human secondary antibodies at a 1:500 dilution for 1 hour at room temperature. After washed with TBST 4 times (5 min each time), added chemiluminescence reagent for 1 min. Then wrapped in plastic wrap, and placed in a cassette with Kodak X-ray film exposure within 1 min. Scaned the X film after developing and fixing, and β-actin as an internal reference.

MTT to detect proliferation ability

The number of attached cells in each well was examined by MTT assay and quantified in a 96 wells plate. Two hundred milliliters of 1640 medium lacking fetal bovine serum and 20 microliters MTT (5 mg/mL) (Sigma, USA) were added to each well. After incubation at 37 °C in 5% CO_2 for 1–7 days, the medium was discarded. One hundred fifty microliters of Dimethyl sulfoxide (DMSO) was added to each well. The amount of MTT formazan product, which reflected the number of cells adhering to FN, was determined by measuring absorbance with a microplate reader at a test wavelength of 570 nm.

Boyden chamber invasion experiment in vitro to detect invasive ability of cells

Polycarbonate microporous membrane invested with artificial rubber basement with aperture 8 μm were unfold between the upper and lower chamber of the Boyden chamber, and aggregated 2 hours at 37 ℃ in incubator. The 200 μL pEGFP-N1-ZNF217/HO-8910, pEGFP-N1/HO-8910 and HO-8910 cells were seeded into the upper part of the chamber. In the lower part of the chamber, RPMI 1640 supplemented with 10% FBS was added. Then, the transwell chamber was put in a humidiied atmosphere of 95% air with 5% CO_2 at 37 ℃. After 48 hours, we took out the membrane filter, fixed with neutral formaldehyde, and observed in HE staining. Counted cell numbers in membrane selected five horizons randomly by the 200 times light microscopy, and took the average to represent the invasive ability of the cells.

In vitro invasion assay

Cell migration was assayed using a Transwell chemo-

taxis chamber (8-μm pore filters). The HO-8910 cells, PEGFP-N1/HO-8910 cells, and PEGFP-N1-ZNF217/HO-8910 cells (10^5 /well) were starved for 24 h. Then these cells were trypsinized and loaded into the top chamber. Ten percent fetal bovine serum was then placed into the bottom chamber as a chemoattractant. Cells were incubated at 37 ℃ in 5% CO_2 for 12 or 24 h and allowed to migrate through the chemotaxis chamber. After incubation, the cells remaining at the upper surface were completely removed. The cells that had migrated to the bottom of the chemotaxis chamber were stained with hematoxylin and eosin. The experiments were repeated in triplicate wells and the migrated cells were counted microscopically (200 ×) in five different fields per filter. Cell invasion capabilities were assessed using a Matrigel invasion chamber (Becton-Dickenson, Bedford, MA, USA) according to the manufacturer's instructions. The procedures were essentially the same as those for the migration assay using Transwell chemotaxis chambers.

Tumorigenicity assay to observe the ability of tumor formation

The pEGFP-N1-ZNF217/HO-8910 and pEGFP-N1/HO-8910 cells in the logarithmic phase made were trypsinized into single cell suspension by trypsin digestion. Washed three times with serum free medium and centrifuged, and then suspended cells with serum free medium and counted cells (3.5×10^5 /mL). The 6 nude mice, 3 animals per group, were injected subcutaneous with 0.1 mL pEGFP-N1-ZNF217/HO-8910 or pEGFP-N1/HO-8910 cells in left and right lower limb each. Subcutaneous tumor formation was observed. After the tumors being visible, weighing nude mice every 5 days to observe the weight change, movement and mental stat. And measure the long diameter and short diameter of tumor size by vernier calipers, to calculate tumor volume fraction [tumor volume = π × long diameter × (short diameter)^2 / 6]. Mice were euthanized at after 30 days, and then we drew the tumor growth curve.

Tumorigenicity assays

Three- to four-week-old female nude mice were purchased from Southern Medical University (Guangzhou, China). Animal studies were conducted in strict accordance with the principles and procedures approved by the Committee on the Ethics of Animal Experiments of Southern Medical University, China. There were four animals in each group. These were hypodermically injected with 3.5×10^6 cells in 100 μL medium. After 30 days, the animals were killed and examined for tumor formation. The 1 mm^3 tumor tissues were harvested and transplanted into the ovaries of the next passage of female nude mice. After 30 days, these animals were sacrificed and examined for tumor formation and metastasis. Tumor volume was calculated using V = 0.5 × (width^2 × length). The expression of ZNF217 was detected by immunohistochemistry.

Statistical analysis

Statistical analyses were performed with SPSS software 13.0. All *P*-values were two-sided. $P < 0.05$ was considered statistically significant.

Results

Results of transfection effect

RT-PCR results showed that the relative expression of ZNF217 mRNA of pEGFP-N1-ZNF217/HO-8910, pEGFP-N1/HO-8910 and HO-8910 cells was 2.53, 2.53 and 1.28, respectively. The expression of ZNF217 mRNA in pEGFP-N1-ZNF217/HO-8910 cells was enhanced significantly (Fig. 2). Western blot showed the same results as the RT-PCR (Fig. 3). Both demonstrated that ZNF2l7 gene transfected HO-8910 cells successfully.

ZNF217 genes affected proliferation of HO-8910 cells *in vitro*

MTT assay showed that the proliferation ability of pEGFP-N1-ZNF217/HO-8910 cells was higher than pEGFP-N1/HO-8910 and HO-8910 cells significantly, and difference was more apparent with the extension of time ($F = 32.050$, $P < 0.001$) (Fig. 4) . The results indicated that ZNF217 promoted the proliferation of HO-8910 cells *in vitro*.

ZNF217 enhanced invasion ability of HO-8910 cells *in vitro*

Boyden chamber invasion experiment showed that all of the three types of cells including pEGFP-N1-ZNF217/HO-8910, pEGFP-N1/HO-8910 and HO-8910 cells could penetrate down to the basement membrane, so that deformed tumor cells could be visible on polycarbonate membrane (Fig. 5). The numbers of migrating pEGFP-N1-ZNF217/HO-8910, pEGFP-N1/HO-8910 and HO-8910 cells were (141.25 ± 13.91) cells /200 × field, (82.50 ± 11.73) cells /200 × field and (81.75 ± 12.12) cells /200 × field, respectively, with a significant difference between them ($F = 29.274$, $P < 0.001$). The results suggested that the invasion ability of HO-8910 ovarian cancer cells were enhanced *in vitro* with transfection of pEGFP-N1-ZNF217.

ZNF217 gene enhanced tumor formation ability of HO-8910 cells *in vivo*

Tumor was formed *in vivo* in two groups after nude mice were inoculated with pEGFP-N1-ZNF217/HO-8910 or pEGFP-N1/HO-8910 cells. The volumes of tumor in nude mice inoculated with pEGFP-N1-ZNF217/HO-8910 or pEGFP-N1/HO-8910 cells were (8.72 ± 14.28) mm^3

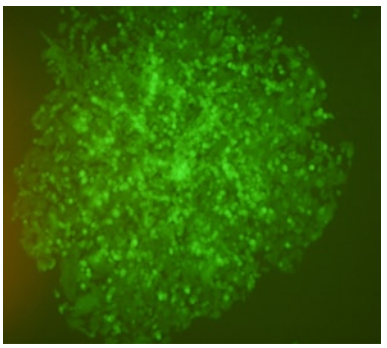

Fig. 1 HO-8910 monoclonal cells with pEGFP-N1-ZNF217 transfected under fluorescence microscope, × 400

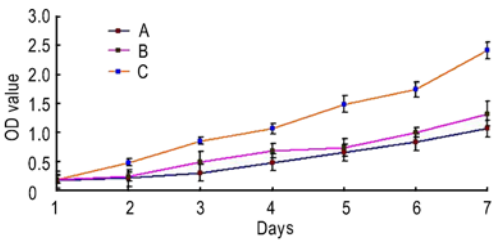

Fig. 4 Growth curves of pEGFP-N1-ZNF217/HO-8910, pEGFP-N1/HO-8910 and HO-8910 cells *in vitro*. A: HO-8910 cells; B: pEGFP-N1/HO-8910 cells; C: pEGFP-N1-ZNF217/HO-8910 cells

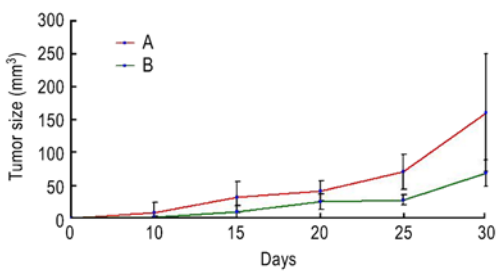

Fig. 6 Growth curves of transplantation tumor in nude mouse inoculated with pEGFP-N1-ZNF217/HO-8910 or pEGFP-N1/HO-8910 cells. A: pEGFP-N1-ZNF217/HO-8910 cells; B: pEGFP-N1/HO-8910 cells

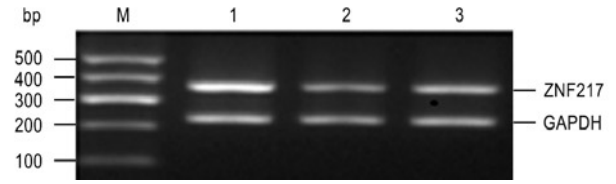

Fig. 2 ZNF217 mRNA in pEGFP-N1-ZNF217/HO-8910, pEGFP-N1/HO-8910 and HO-8910 cells by RT-PCR. M: DNA marker; 1: pEGFP-N1-ZNF217/HO-8910 cell; 2: HO-8910 cell; 3: pEGFP-N1/HO-8910 cell

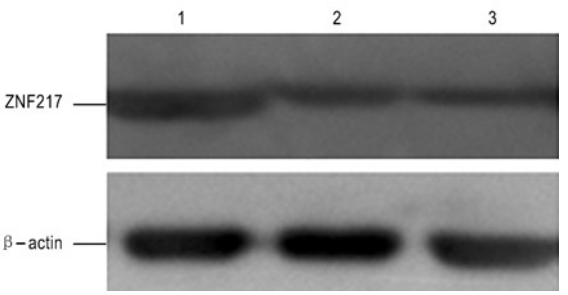

Fig. 3 ZNF217 protein expression in pEGFP-N1-ZNF217/HO-8910, pEGFP-N1/HO-8910 and HO-8910 cells by Western blot. 1: pEGFP-N1-ZNF217/HO-8910 cell; 2: HO-8910 cell; 3: pEGFP-N1/HO-8910 cell

and (0.70 ± 1.71) mm^3 with no significant difference 10 days after inoculation ($P = 0.229$). The volumes of tumor in nude mice inoculated with pEGFP-N1-ZNF217/HO-8910 or pEGFP-N1/HO-8910 cells were (70.30 ± 26.33) mm^3 and (27.39 ± 7.92) mm^3 with a significant difference between them 25 days after inoculation ($P = 0.003$). The volumes of tumor in nude mice inoculated with pEGFP-N1-ZNF217/HO-8910 or pEGFP-N1/HO-8910 cells were (160.49 ± 89.45) mm^3 and (68.21 ± 20.17) mm^3 with a significant difference between them 30 days after inoculation ($P = 0.013$) (Fig. 6). The data indicated that *in vivo* tumor formation ability of pEGFP-N1-ZNF217/HO-8910 cells was significantly higher than that of pEGFP-N1/HO-8910 cells.

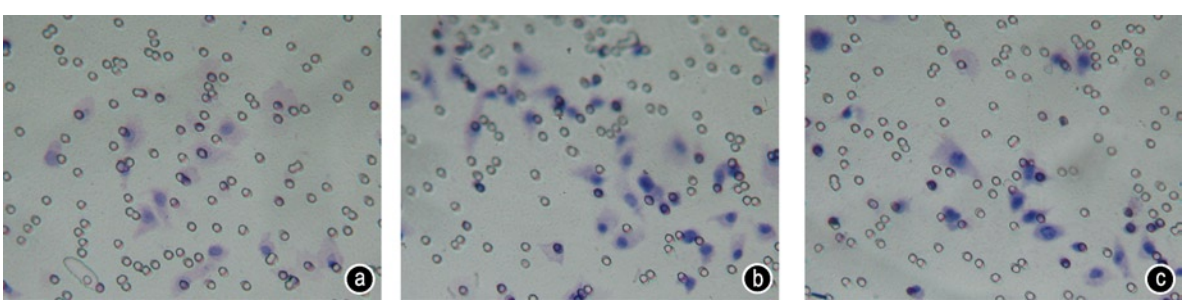

Fig. 5 Boyden chamber invasion experiment to detect invasion ability of pEGFP-N1-ZNF217/HO-8910, pEGFP-N1/HO-8910 and HO-8910 cells *in vitro*. a: HO-8910 cells; b: pEGFP-N1/HO-8910 cells; c: pEGFP-N1-ZNF217/HO-8910 cells

Discussion

ZNF217 is a putative oncogene believed to encode an alternatively spliced Krüppel-like transcription factor. ZNF217 gene belonged to the zinc-finger protein family located on chromosome 20q13.2 is an epithelial tumors candidate newly discovered [2–3]. Zinc-finger protein is one of the most typical and important DNA binding proteins, most of which have an approved signal. Zinc-finger proteins play as nuclear transcription factors in a cell can introduce into the nucleus through the nuclear pores regulating the expression of other genes [4]. Quinlan *et al* found that ZNF217 is a transcription inhibiting factor in the experiments of human malignant multiple teratoma cells NTERA-2 [5]. Invasion and metastasis related target genes including tumor cell adhesion genes, extracellular matrix protein genes, cell growth and proliferation genes, cell cycle regulation genes, transcription factors, regulate genes and apoptosis genes, etc [6]. Our recent results showed that ZNF217 is associated with poor prognosis and enhances proliferation and metastasis in ovarian cancer [7]. And ZNF217 genes is likely to be involved in tumor occurrence and development process as a transcriptional regulation factor [7]. In recent years, some research results also showed that ZNF217 genes involved in occurrence and development process of esophageal squamous carcinoma, gastric cancer, prostate cancer and colorectal cancer [8–12]. ZNF217 overexpression is critical to growth and survival of ovarian clear cell carcinoma with ZNF217 gene amplification [13]. Especially in the research of gastric cancer and colorectal cancer, the scholars found that the ZNF217 gene amplification is related to poor prognosis of patients and the invasion of tumor [14–18]. Our preliminary results also showed that amplification of ZNF217 gene is associated with differentiation and clinical stage of ovarian cancer. The worse of differentiation and the later of clinical stage, the greater chance of amplification of ZNF217 gene [1]. The above findings suggested ZNF217 gene may plays an important role in the process of initiation and progression in malignant tumor, especially in the epithelial tumors. Recently, it has been reported that ZNF217 amplification occurs in a variety of tumor types, such as breast, gastric, ovarian, lung, prostate, and colon cancer, and is associated with aggressive tumor behavior.

Epithelial ovarian cancer is the most common ovarian malignant tumor. In order to study the relationship between ZNF217 gene expression and occurrence and development of ovarian cancer, ZNF217 gene was transfected into human ovarian cancer HO-8910 cell lines, and detected transfection efficiency by RT-PCR and Western blot methods. Results showed that the expressions of ZNF217 mRNA and protein were high in HO-8910 cells after transfection. MTT results indicated that ZNF217 promoted the proliferation of HO-8910 cells *in vitro*. Boyden chamber assay showed that invasion ability of HO-8910 ovarian cancer cells was enhanced *in vitro* with transfection of ZNF217. The nude mouse experiment showed that the *in vivo* tumor formation ability of pEGFP-N1-ZNF217/HO-8910 cells was significantly higher than that of pEGFP-N1/HO-8910 cells. The above findings indicated that with the increased of expression of ZNF217, HO-8910 cell cycle progress will be accelerated, and cell proliferation, invasion and metastasis will be promoted. Therefore, ZNF217 gene is likely to be a promote factors in cancerous changing of ovarian epithelial cells, invasion and metastasis of ovarian cancer.

ZNF217 protein localizes in both the nuclear and cytoplasmic cellular compartments. The study reported that ZNF217 is a new interacting and functional partner of the ERa hinge region, which applicated that high expression levels of ZNF217 in ER+/luminal breast cancer samples are associated with altered estrogen signalling and altered endocrine therapy responses [19]. Recently, Krig *et al* reported that ZNF217 regulates expression of ErbB3, which results in the activation of the PI3K-AKT pathway in breast cancer cells [20]. Interestingly, the present results indicated that ZNF217 amplification and PIK3CA mutation were almost mutually exclusive. Therefore, ZNF217 amplification may activate PI3K-AKT signaling via ErbB3 activation [13]. Further examination is required to clarify these hypotheses of molecular mechanisms that ZNF217 plays.

Based on these clinical and laboratory observations, we conclude that ZNF217 may contribute to ovarian cancer invasion and metastasis, and associated with worse clinical outcomes. We evaluated ZNF217's role as a biomarker of ovarian carcinogenesis and tumor progression in patient samples and explored possible molecular mechanisms in promoting tumor growth and invasion.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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