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Investigation of miR-93-5p and its effect on the radiosensitivity of breast cancer

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ABSTRACT

Accumulating evidence suggests that intrinsic resistance to radiotherapy reduces the survival of patients with cancer. The present study investigated whether miR-93-5p affects proliferation, migration, apoptosis, and radiosensitivity of breast cancer (BC) cells. MDA-MB-468, MCF-7, and MDA-MB-231 BC cells were incubated with hsa-miR-93-5p mimics, hsa-miR-93-5p inhibitor, and negative control RNA with or without exposure to ionizing radiation to determine cell proliferation, migration, and apoptosis using the Cell Counting Kit-8 assay, wound healing assay and apoptotic assay, respectively. Overexpression of miR-93-5p inhibited the migratory abilities (P = 0.001) and decreased the cell proliferation (P = 0.049) of MCF-7 cells. In MCF-7 cells, a significant increase in apoptosis was detected after treatment with miR-93-5p compared with the negative control (P = 0.001) and miR-93-5p inhibitor (P = 0.004). In MDA-MB-468 cells, the proportion of apoptotic cells increased following exposure to ionizing radiation (P = 0.001). The percentage of apoptotic MDA-MB-231 cells in the miR-93-5p group was significantly increase compared with that determined in the negative control (P = 0.044) and hsa-miR-93-5p inhibitor (P = 0.046) groups. In conclusion, our findings showed that miR-93-5p reduces BC cell proliferation and migratory capacity, and increases the ratio of apoptotic cells. Overexpression of miR-93-5p could increase radiosensitivity in BC cells by increasing apoptosis. This evidence provides new insight into the treatment of BC and identifies miR-93-5p as a potential therapeutic target.

Introduction

Breast cancer (BC) is the most malignant and leading cause of death in women. According to an estimation from the United States of America, approximately 279,100 new BC cases will be diagnosed in 2020 [1]. Radiation therapy is one of the primary treatments of BC. For patients with early-stage BC, the effectiveness of mastectomy is generally similar to that of breast-conserving surgery followed by radiotherapy [2]. However, due to the insensitivity of BC cells to ionizing radiation (IR), radiotherapy cannot eradicate BC cells. In addition, an increase in the dose of radiotherapy often damages normal tissue. Therefore, the identification of new drugs, which sensitize BC cells to radiation, is urgently warranted to reduce therapeutic doses, enhance radiotherapeutic response in cancers, and mitigate toxicity in normal tissue.

According to a large number of studies, the carcinogenesis of BC is associated with genetic and epigenetic alterations. Currently, the importance of microRNAs (miRNAs) in human cancers is attracting considerable interest. These are a class of small (~22 nucleotides in length) non-coding RNA molecules, which control gene expression by seeding match in the 3′untranslated-region of target mRNAs, resulting in gene silencing [3]. We detected the expression of exosomal miR-93-5p in the plasma of BC, and found that miR-93-5p was significantly enriched in exosomes [4]. Chu et al. found that miR-93-5p was involved in inducing epithelial–mesenchymal transition and drug resistance in BC cells [5]. Li et al. reported that miR-93-5p induced migration, invasion, and proliferation in MCF-7 BC cells [6]. Taken together, these data indicate that miR-93-5p plays an important role in BC. However, the potential radiosensitizing effects of miR-93-5p remain unclear.

The objective of the present study was to investigate the role of miR-93-5p in MDA-MB-468,

MCF-7, and MDA-MB-231 BC cells after exposure to IR.

Materials and methods

Cell lines and culture conditions

The BC cell lines (MDA-MB-468, MCF-7, and MDA-MB-231) were obtained from the American Type Culture Collection. The cells were cultured in Dulbecco's modified Eagle's medium (DMEM; GIBCO, Grand Island, NY, USA) with 4.5 g/L d-glucose, l-glutamine, 110 mg/L sodium pyruvate, containing 10% fetal bovine serum (FBS; GIBCO), 100 units/mL penicillin, and 0.1 mg/mL streptomycin. All cells were maintained in a humidified incubator at 37°C with 5% CO_2. Subsequent experiments were performed as the cells reached the logarithmic growth phase.

Transfection

Transfection was performed with a Lipofectamine 2000 kit (Invitrogen, Carlsbad, CA, USA) according to the instructions provided by the manufacturer. Double-stranded hsa-miR-93-5p mimics (miR-93-5p; Biomics Biotech, Nantong, China), single-stranded hsa-miR-93-5p inhibitor (miR-93-5p inhibitor; Biomics Biotech), and their relative negative control RNA (negative control; Biomics Biotech) were introduced into cells at a final concentration of 10, 50, and 10 μM, respectively. The sequences of miR-93-5p for the sense and anti-sense strands were 5′-CAAAGUGCU GUUCGUGCAGGUAG-3′ and 5′-CUAC CUGCACGAACAGCACUUUG-3′, respectively. The sequences of miR-93-5p inhibitor for the anti-sense strands were 5′-CUACCUGCACGAACAGCACUUUG-3′. The cells were transfected in DMEM without FBS for 6 h, which was replaced with DMEM containing 10% FBS.

Irradiation

After the cells were seeded in six- or 96-well plates for 24 h, BC cells in the IR group were exposed to radiation (2 Gy dose; 60Co-gamma rays, dose rate: 200 cGy/min) by linear accelerator (Varian Medical Systems, San Francisco, California, USA) in the irradiation center of Jiangsu Taizhou People's Hospital, Hospital Affiliated 5 to Nantong University.

Migration assay

A scratch assay was performed in MDA-MB-468, MCF-7, and MDA-MB-231 cells. The cells were seeded in six-well plates, cultured to form a monolayer, left to adhere for 4 h, and scraped with a 10 μL pipette tip at the center of the well. FBS-free medium was prepared to avoid the effect of growth factors and prevent proliferation. One group was exposed to IR (2 Gy), while the other group was used as control. The cells were gently washed twice with PBS, and the plates were replenished with FBS-free medium. The images of cells were captured at 0, 6, 12, and 24 h using a 5× microscope lens (CKX41 microscope, Olympus Corporation, Shinjuku, Tokyo, Japan). The total area of migrated cells was calculated using the ImageJ 1.8.0 (National Institutes of Health, Bethesda, MD, USA) software [7]. The cell migration was quantified by determining the extent (%) of wound healing as follows: (0 h scratch area – 24 h scratch area)/0 h scratch area × 100%. The experiment was performed in triplicate.

Cell viability assay

Cell viability assay was assessed with the Cell Counting Kit-8 (CCK8; Dojindo, kumamoto, Japan) assay according to the instructions provided by the manufacturer. MDA-MB-468, MCF-7, and MDA-MB-231 cells were seeded in 96-well plates at a density of 5×10^3, 2×10^3, and 8×10^3 cells per well in triplicate, respectively. Cells were cultured for 6 h to attach to the plates and transfected with miR-93-5p or miR-93-5p inhibitor or negative control, together with 2.5 nM of the Lipofectamine 2000 kit reagent (Invitrogen). One group was exposed to IR (2 Gy), while the other group was used as control. Following transfection (24, 48, and 72 h) with miR-93-5p, miR-93-5p inhibitor, or negative control, 10 μL of CCK8 was added to each well for 1 h at 37°C. Subsequently, optical density was measured at 450 nm on

a microplate reader (Tecan, Männedorf, Switzerland). Each experiment was repeated thrice with triplicate wells [8].

Apoptosis assay

MDA-MB-468, MCF-7, and MDA-MB-231 were seeded in six-well plates at a density of 5×10^5, 3×10^5, and 2×10^5 cells per well in triplicate, respectively. After 6 h, cells were transfected with miR-93-5p, miR-93-5p inhibitor, or negative control. One group was exposed to IR (2 Gy), while the other group was used as control. Following incubation of BC cells for 24 h, 25 µM topoisomerase I inhibitor camptothecin was introduced into cells for 4 h as an apoptotic positive control. The Annexin V-FITC/PI Apoptosis Detection Kit I (Solarbio, Science & Technology, Beijing, China) was used according to the instructions provided by the manufacturer for the detection of camptothecin- and miRNA-mediated apoptosis. The cell apoptosis was measured on a FACSalibur flow cytometer (BD Biosciences, San Jose, CA, USA) [8].

Statistical analysis

Quantitative data were expressed as the mean ± standard deviation. The data were assessed by one-way analysis of variance using the SPSS version 18.0 statistical software (IBM Corp., Armonk, NY, USA). $P < 0.05$ denoted statistically significant differences.

Results

Overexpression of miR-93-5p inhibited the migration of BC cells under IR

The migration assays were performed to investigate the effect of miR-93-5p on the migratory abilities of BC cell lines. MDA-MB-468, MCF-7, and MDA-MB-231 cells were classified into the negative control, miR-93-5p, and miR-93-5p inhibitor groups, respectively. It was observed that overexpression of miR-93-5p inhibited the migratory abilities (P = 0.001) of MCF-7 cells (Figure 1 (a,b)). Moreover, following exposure of this cell line to IR, miR-93-5p inhibitor increased the

percentage of wound healing areas (P = 0.001) (Figure 1(a,b)). A similar result was recorded in MDA-MB-231 BC cells (P = 0.039) (Figure 1(c)).

Overexpression of miR-93-5p repressed cell proliferation

The cell viability of BC cells was detected by CCK-8 assays. The results demonstrated that overexpression of miR-93-5p decreased cell proliferation in MCF-7 BC cells (P = 0.049) (Figure 2(a)). Following exposure of this cell line to IR, cell growth in the miR-93-5p group was decreased (P = 0.001) (Figure 2(a)). Additionally, we found that the cell viability of MDA-MB-468 cells (P = 0.005) and MDA-MB-231 cells (P = 0.001) was decreased after exposure to IR (Figure 2(b,c)). Similar results were also observed after overexpression of miR-93-5p (P = 0.025, P = 0.032).

Overexpression of miR-93-5p and IR induced apoptosis in BC cells

The apoptosis assay following transfection with the miR-93-5p mimic and exposure to IR was performed in MDA-MB-468, MCF-7, and MDA-MB-231 cells (Figure 3(a,b), 4(a,b), 5(a,b)).

In MDA-MB-468 cells, the ratio of apoptotic cells was markedly increased, as shown by annexin V-fluorescein isothiocyanate/propidium iodide (annexin V-FITC/PI) staining following exposure to IR with or without camptothecin (P = 0.001) (Figure 3(c)). A significant decrease in apoptosis was detected in the miR-93-5p inhibitor treatment group compared with that noted in the negative control (P = 0.007) (Figure 3(d)). Furthermore, a significant decrease in apoptosis was observed in the miR-93-5p inhibitor group compared with the camptothecin (negative control) group (P = 0.001) (Figure 3(e)). Moreover, miR-93-5p inhibitor combined with camptothecin decreased apoptosis compared with the negative control (P = 0.001) (Figure 3(e)).

In MCF-7 cells, the percentage of apoptotic cells was markedly decreased in the miR-93-5p inhibitor group compared with the miR-93-5p group (P = 0.04) (Figure 4(c)). A significant decrease in apoptosis was detected following treatment with miR-93-5p inhibitor versus the negative control
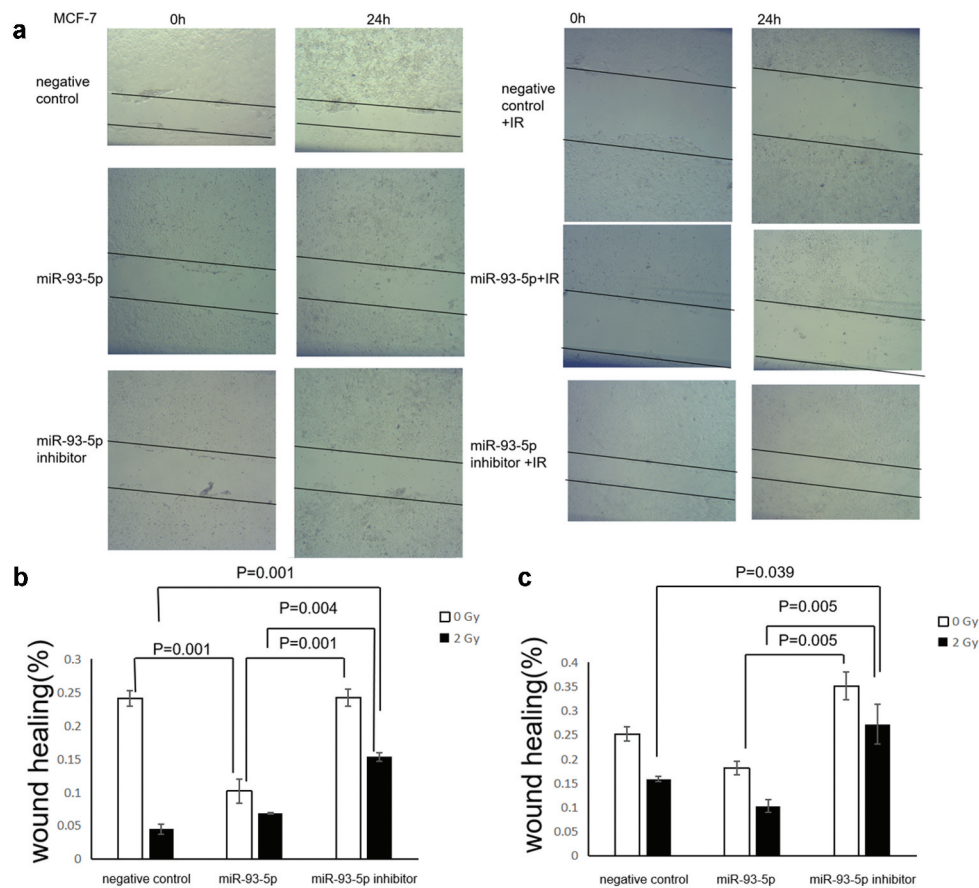
Figure 1. Migration assay results for BC cells. Overexpression of miR-93-5p inhibits migration in MCF-7 and MDA-MB-231 BC cells. The wound healing assay was conducted to determine: (a) the migratory and (b) invasive abilities of each group in MCF-7 cells, and (c) the invasive ability of each group in MDA-MB-231 cells.

BC, breast cancer

(P = 0.008) and miR-93-5p (P = 0.04) with camptothecin (Figure 4(c)). For further verification, the induction of apoptosis by IR combined with camptothecin was measured in MCF-7 cells transfected with miR-93-5p, miR-93-5p inhibitor, or the negative control. A significant increase in apoptosis was detected following treatment with miR-93-5p compared with the negative control (P = 0.001) and miR-93-5p inhibitor (P = 0.004) (Figure 4(d)). We also found that miR-93-5p combined with camptothecin significantly increased the percentage of apoptotic cells versus IR combined with camptothecin (P = 0.001) and IR combined with miR-93-5p (P = 0.001) (Figure 4(e)).

In MDA-MB-231 cells, the percentage of apoptotic cells was markedly increased in the IR group (P = 0.001) (Figure 5(c)). A significant increase in apoptosis was detected in the IR combined with miR-93-5p group versus the miR-93-5p (P = 0.001)

and miR-93-5p combined with camptothecin (P = 0.002) groups (Figure 5(c)). Similar to MCF-7 cells, the percentage of apoptotic MDA-MB-231 cells in the miR-93-5p group was significant increased compared with that noted in the negative control (P = 0.044) and miR-93-5p inhibitor (P = 0.046) groups (Figure 5(d)). Following exposure of this cell line to IR, a significant increase was also observed in the miR-93-5p group compared with the negative control (P = 0.005) and miR-93-5p inhibitor (P = 0.033) groups. This increase was also detected after the addition of camptothecin (P = 0.001 in both groups). Treatment with miR-93-5p combined with IR significantly increased the number of apoptotic cells in MDA-MB-231 cells compared with IR alone and miR-93-5p alone (Figure 5(f)). These findings demonstrated that overexpression of miR-93-5p in cells was correlated with increased sensitivity to IR (Figures 3–5).
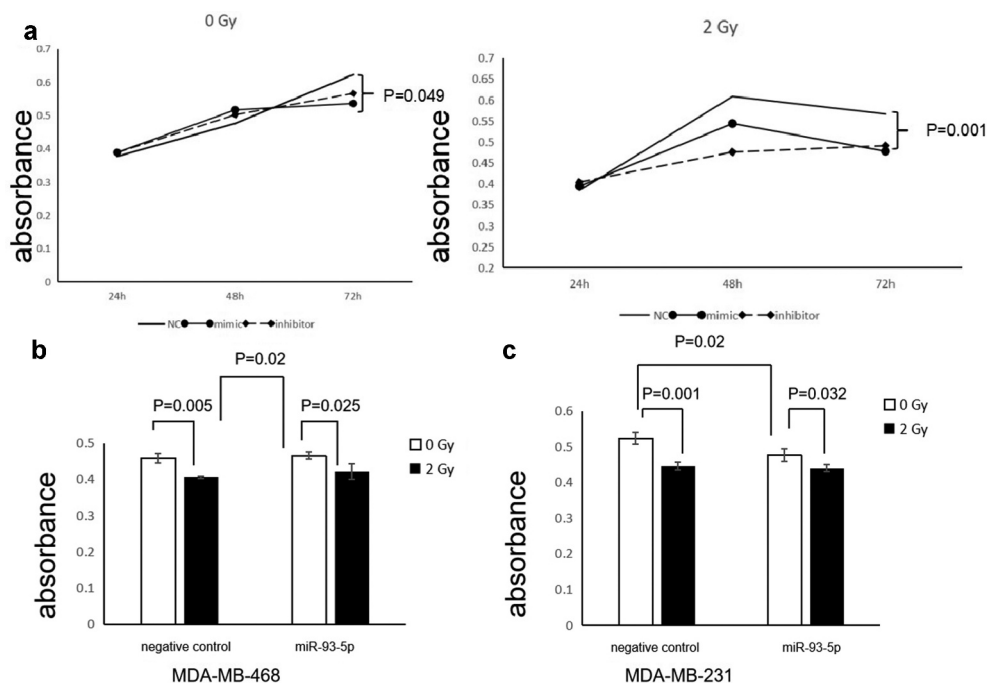
Figure 2. Cell viability assay results for BC cells. BC cells were transiently transfected with a negative control, miR-93-5p mimic, or miR-93-5p inhibitor. After 24, 48, and 72 h, cells were treated with CCK8. Cell proliferation after overexpression and inhibition of miR-93-5p was measured at an absorbance of 450 nm. The standard deviations from triplicate experiments are indicated in the line chart. (a) Cell viability was determined at different time points exposed with or without IR in MCF-7 cells. (b) Column bar graph showing that the cell viability of MDA-MB-468 cells was inhibited by IR. (c) Column bar graph showing that the cell viability of MDA-MB-231 cells was inhibited by miR-93-5p without IR, while that of MDA-MB-231 cells was inhibited by IR with or without miR-93-5p.

BC, breast cancer; CCK8, Cell Counting Kit-8; IR, miR-93-5p inhibitor, hsa-miR-93-5p inhibitor; IR, ionizing radiation; miR-93-5p, hsa-miR-93-5p mimics

Discussion

MiRNA is involved in numerous biological pathways by regulating a series of protein-coding genes [9]. In a previous study, we found that miR-93-5p was overexpressed in exosomes obtained from patients with ductal carcinoma in situ [4]. Huang et al. found that miR-93-5p antagomir enhanced the sensitivity of small cell lung cancer cells to chemotherapy [10]. Wu et al. suggested that miR-93-5p is a central regulator of immune escape [11]. In our study, we investigated the role of miR-93-5p in MDA-MB-468, MCF-7, and MDA-MB -231 BC cells. We found that overexpression of miR-93-5p in MCF-7 cells inhibited their migratory ability, decreased proliferation, and increased the ratio of apoptotic cells. However, in the present study, the effects of miR-93-5p in MDA-MB -231 BC cells was only of borderline statistical significance. Moreover, the percentage of apoptotic MDA-MB-231 cells in the miR-93-5p group was significantly increased. Meanwhile, in MDA-

MB-468 cells, a significant decrease in apoptosis was detected in the miR-93-5p inhibitor group compared with the negative control group. The difference in results may be attributed to the different characteristics of BC cell lines. MCF-7 cells have functional estrogen and are noninvasive, whereas MDA-MB-231 cells are a model for more aggressive, hormone-independent BC [12].

We found that IR arrested proliferation in MDA-MB-231 cells, with and without overexpression of miR-93-5p (Figure 2(c)). This finding indicated that the addition of miR-93-5p had no effect on the inhibition of proliferation induced by IR. Therefore, the regulation of gene expression through miRNA may be a promising therapeutic method [13].

The development of a radiation-resistant tumor cell population may be partly responsible for the disease recurrence experienced by 10–15% of patients with BC after breast-conserving strategy [14]. Therefore, improving radiosensitivity in BC
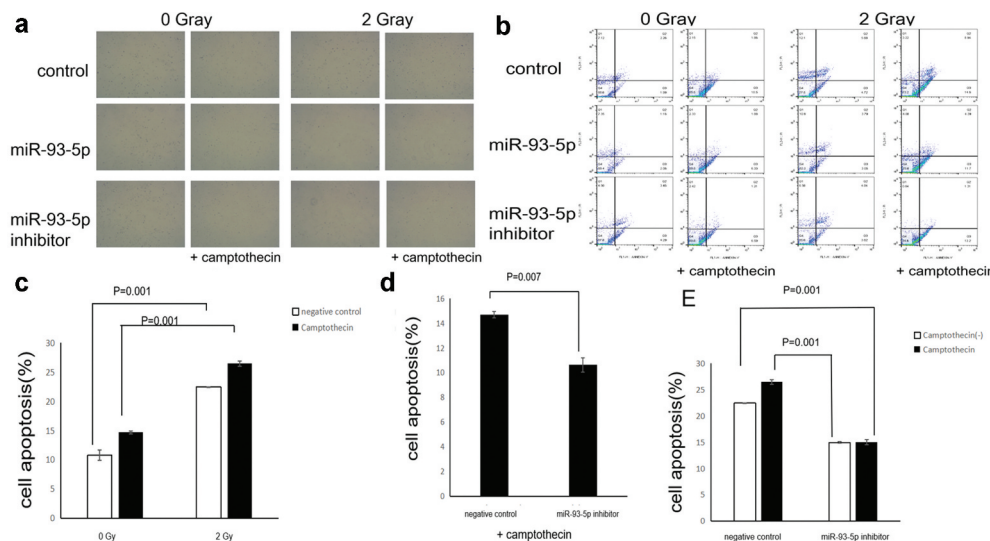
Figure 3. Apoptosis assay results for MDA-MB-468 cells. (a) The images of MDA-MB-468 cells were induced by negative control, miR-93-5p, and miR-93-5p inhibitor with IR or camptothecin, respectively. (b) Apoptosis was measured by annexin V-FITC/PI staining and analyzed with flow cytometry. (c) Column bar graph showing that IR induced apoptosis in MDA-MB-468 cells with or without Camptothecin. (d) Column bar graph showing that apoptosis of MDA-MB-468 cells was inhibited by miR-93-5p inhibitor loaded with camptothecin. (e) Column bar graph showing that apoptosis of MDA-MB-468 cells was induced by miR-93-5p inhibitor and camptothecin. Error bars indicate the mean ± SD.

FITC/PI, fluorescein isothiocyanate/propidium iodide; miR-93-5p inhibitor, hsa-miR-93-5p inhibitor; IR, ionizing radiation; miR-93-5p, hsa-miR-93-5p mimics; SD, standard deviation
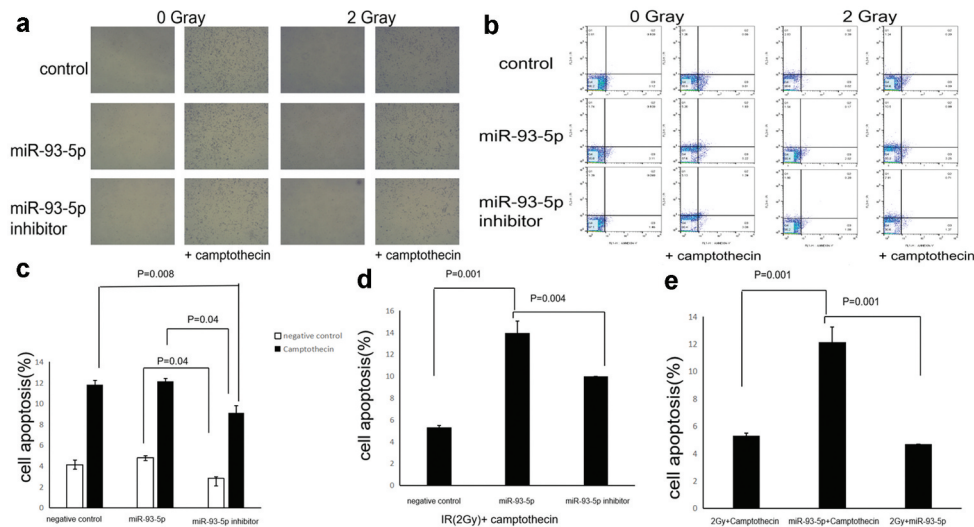

Figure 4. Apoptosis assay results for MCF-7 cells. (a) The images of MCF-7 cells were induced by negative control, miR-93-5p, and miR-93-5p inhibitor with IR or camptothecin, respectively. (b) Apoptosis was measured by annexin V-FITC/PI staining and analyzed with flow cytometry. (c) Column bar graph showing that apoptosis of MCF-7 cells was inhibited by miR-93-5p inhibitor. (d) Column bar graph showing that apoptosis of MCF-7 cells was induced by miR-93-5p, whereas it was inhibited by miR-93-5p inhibitor loaded with camptothecin and exposure to IR. (e) The effect of IR combined with miR-93-5p or camptothecin on the induction of apoptosis in MCF-7 cells was weaker than that of miR-93-5p combined with camptothecin. Error bars indicate the mean ± SD.

FITC/PI, fluorescein isothiocyanate/propidium iodide; miR-93-5p inhibitor, hsa-miR-93-5p inhibitor; IR, ionizing radiation; miR-93-5p, hsa-miR-93-5p mimics; SD, standard deviation

remains a challenge. Numerous studies have shown that miRNA has the ability to alter the radiosensitivity of cancer cells. For example, therapeutic delivery of miR-29b enhances the radiosensitivity of cervical cancer [15]. Moreover, miR-145 may assist in overcoming resistance to radiotherapy in colorectal cancer [16]. Furthermore, Lin et al. found that miR-200 c
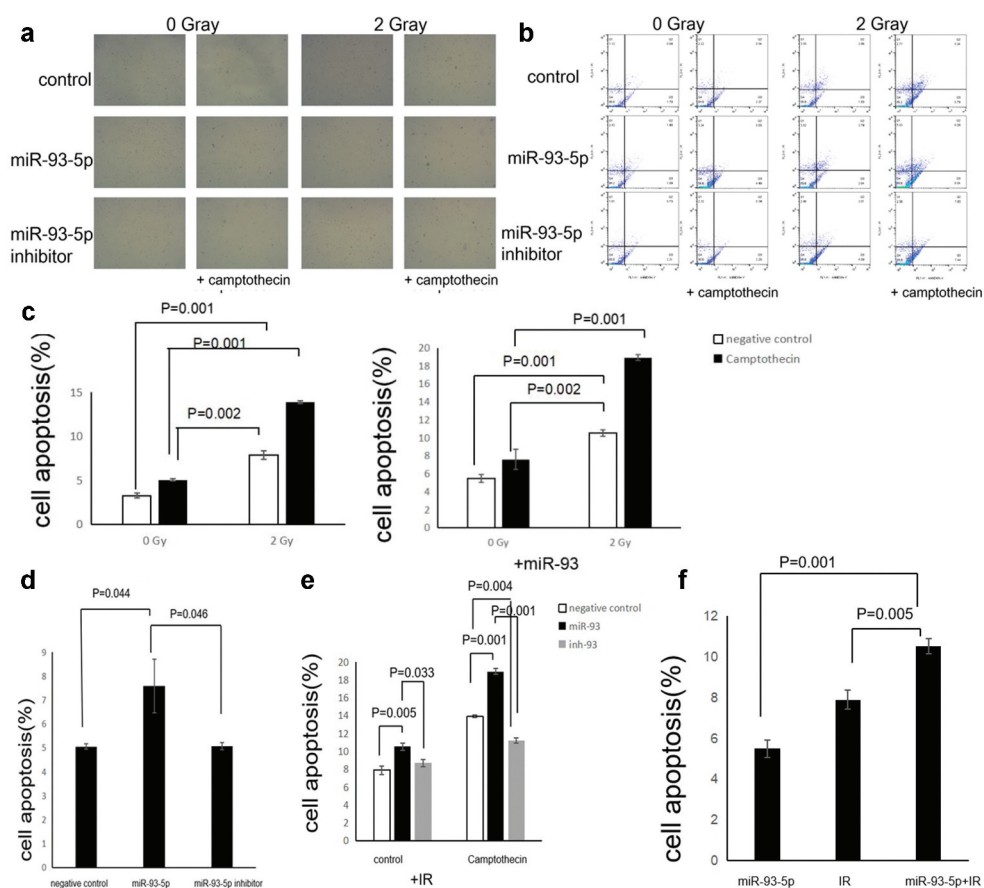
Figure 5. Apoptosis assay results for MDA-MB-231 cells. (a) The images of MDA-MB-231 cells were induced by negative control, miR-93-5p, and miR-93-5p inhibitor with IR or camptothecin, respectively. (b) Apoptosis was measured by annexin V-FITC/PI staining and analyzed with flow cytometry. (c) Column bar graph showing that IR induced apoptosis in MDA-MB-231 cells with or without miR-93-5p. (d) Column bar graph showing that apoptosis of MDA-MB-231 cells was induced by miR-93-5p, whereas it was inhibited by miR-93-5p inhibitor loaded with camptothecin. (e) Column bar graph showing that apoptosis of MDA-MB-231 cells was induced by miR-93-5p, whereas it was inhibited by miR-93-5p inhibitor with or without camptothecin and exposure to IR. (f) The effect of IR combined with miR-93-5p on the induction of apoptosis in MDA-MB-231 cells was stronger than that of IR or miR-93-5p alone. Error bars indicate the mean ± SD.

FITC/PI, fluorescein isothiocyanate/propidium iodide; miR-93-5p inhibitor, hsa-miR-93-5p inhibitor; IR, ionizing radiation; miR-93-5p, hsa-miR-93-5p mimics; SD, standard deviation.

enhances the radiosensitivity of BC cells [17]. However, the relationship between miR-93-5p and IR had not been previously investigated. Therefore, in the present study, we also analyzed the effects of miR-93-5p on MDA-MB-468, MCF-7, and MDA-MB-231 BC cells exposed to IR. Our findings showed, for the first time, an association of miR-93-5p with radiosensitivity. We found that the combination of IR and miR-93-5p strongly influenced the induction of apoptosis in MDA-MB-231 and MCF-7 cells compared with their individual effects. However, similar results were not observed in other BC cell lines. This discrepancy could be explained by differences in the radiosensitivity of BC cell lines. Based on these

findings, miR-93-5p may become a potential therapeutic target in patients with BC. Further follow-up analyses are warranted to investigate the mechanism of this miRNA in radiotherapy of BC. Particularly, it has been shown that the autophagy regulatory network [18], DNA damage response [19], and IL8/AKT signaling axis [20] are involved in cancer radiosensitivity.

We found that miR-93-5p inhibitor increased the percentage of wound healing areas in MCF-7 and MDA-MB-231 BC cell lines after IR. This result indicated that IR could enhance the effect of miR-93-5p. Moreover, compared with IR or miR-93-5p alone, their combination significantly increased apoptosis in MDA-MB-231 cells. These

results suggest synergy between IR and miRNA therapies and provide directions for further investigation.

In conclusion, our findings showed that miR-93-5p reduces the proliferation and migratory capacity of BC cells, and increases the ratio of apoptotic cells. Overexpression of miR-93-5p may increase radiosensitivity in BC cells by increasing apoptosis. This evidence provides new insight into the treatment of BC, and identifies miR-93-5p as a potential therapeutic target.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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