

MicroRNA-26b suppresses autophagy in breast cancer cells by targeting DRAM1 mRNA, and is downregulated by irradiation

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Abstract. MicroRNAs (miRs) are small RNAs that do not code for proteins, but instead decrease the stability and suppress the translation of target mRNAs by binding with complementary sequences in their 3'-untranslated regions (3'-UTRs). In the present study, it is reported that breast cancer tumor tissue, as well as irradiated MCF7 breast cancer cells, exhibit decreased levels of miR-26b expression compared with normal breast tissue and MCF7 cells without exposure to radiation. Additionally, a luciferase reporter assay was used to demonstrate that miR-26b directly targets DNA damage-regulated autophagy modulator 1 (DRAM1). MCF7 cells that were transfected with an miR-26b mimic exhibited the downregulated expression of DRAM1 protein and a reduced level of irradiation-induced autophagy. Inhibiting miR-26b resulted in the upregulation of DRAM1 and increased levels of irradiation-induced autophagy in MCF7 cells. These results suggest that therapeutic strategies to target miR-26b may increase the efficacy of certain types of cancer therapy.

Introduction

MicroRNAs (miRNAs/miRs) typically contain 20-24 nucleotides and do not code for proteins, but instead modulate the expression of specific target genes. miRNAs bind to 3'-untranslated regions of target mRNA molecules to repress translation or enhance degradation (1). As each miRNA has multiple targets, a single microRNA may produce diverse

effects by functioning as a tumor initiator or suppressor (2). miRNAs may regulate various critical signaling networks to modulate carcinogenesis (3-6). The differential expression of miR-26b has been demonstrated in several types of tumor, including lung (7), cervical (8), tongue (9) and breast cancer (10), suggesting that it has specific roles in tumor pathology. Previous studies conducted with clinical samples of breast tumor tissue have indicated that miR-26b may inhibit tumor formation, and that its overexpression induces apoptosis and inhibits proliferation (10-12).

DNA damage-regulated autophagy modulator 1 (DRAM1) is a lysosomal protein upregulated by p53 that induces the macro-autophagy activity associated with cell death; DRAM1 is critical for the induction of programmed cell death, contributing to the tumor-suppressive effects of p53 (13-15).

Despite the previous studies on miR-26b, the functions of miR-26b and its target genes remain to be fully characterized, including in human breast cancer. In the present study, the function of miR-26b in breast cancer was determined using the human breast cancer cell line MCF7. The results of the present study demonstrated low-expression of miR-26b in breast cancer tumor tissue. In addition, it was identified that miR-26b downregulated DRAM1 by targeting the 3'-UTR directly. Inhibiting miR-26b upregulated DRAM1 and increased irradiation-induced autophagy. Therefore, the results of the present study may provide a novel insight for targeting therapy of cancer.

Materials and methods

Tissue samples. Three paired samples of breast cancer tissue and adjacent noncancerous tissue were provided by the Breast and Thyroid Surgery Department of the China-Japan Union Hospital (Changchun, China) between June 2013 and December 2013, with a mean age of 41 years (range, 37-49 years). All samples of breast cancer tissue had been pathologically confirmed as invasive ductal carcinoma. None of the patients had been treated with chemotherapy or radiation therapy prior to surgery. The study was approved by the China-Japan Union Hospital of Jilin University and informed, written consent was provided by all patients.

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Cell culture and transfection. Human MCF7 breast cancer cells were purchased from the Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences (Beijing, China) and cultured at 37°C in Dulbecco's Modified Eagle's Medium (DMEM; Gibco; Thermo Fisher Scientific, Inc., Waltham, MA, USA) containing fetal bovine serum (10%; HyClone; GE Healthcare, Logan, UT, USA), penicillin (100 units/ml), and streptomycin (100 units/ml), in a humidity-controlled incubator with an atmosphere containing 5% CO₂. Following culture, the cells were transfected with 100 nmol of an miR-26b mimic or inhibitor, or a negative control miRNA (NC; GenePharma, Shanghai, China) using Lipofectamine™ 2000 (Invitrogen; Thermo Fisher Scientific, Inc.) according to the manufacturer's protocol; they were then exposed to ionizing radiation (IR) as subsequently described. The NC was designed not to target any human gene. The sequence for the miR-26b mimic was sense, 5'-UCAAGUAAUUCAGGAUAG GU-3', antisense, 5'-CUAUCCUGAAUUAUUGAAU-3'; the sequence for the miR-26b inhibitor was sense, 5'-ACCUAU CCUGAAUUAUUGAA-3', antisense, 5'-CAGUACUUU UGUGUAGUACAA-3'; the sequence for the NC was sense, 5'-UUCUCCGAACGUGUCACGUTT-3', antisense, 5'-ACG UGACACGUUCGGAGAATT-3'. Specific siRNAs for human DRAM (catalog no. sc-96209) and control siRNA (catalog no. sc-44230) were purchased from Santa Cruz Biotechnology, Inc. (Dallas, TX, USA).

Irradiation. Cells were given for IR 24 h after transfection and harvested by centrifugation at 13,201 x g for 3 min at room temperature for analysis. IR was delivered at a rate of 0.38 Gy/min (180 kV; 18 mA) using an XSZ-Z20/20 X-ray generator (Kang Jia Instrument Equipment Co., Ltd., Dandong, China).

Detection of miR-26b by reverse transcription-quantitative polymerase chain reaction (RT-qPCR). At 48 h after transfection, total cellular RNA was extracted using the TRIzol reagent (Invitrogen; Thermo Fisher Scientific, Inc.). The RNA samples were then frozen at -80°C until use in further analyses. The expression of miRNA was detected using a Hairpin-it™ miRNAs RT-PCR Quantization kit, containing miR-26b primers and U6 primers (E22002; GenePharma) and an MX3000p thermocycler (Stratagene; Agilent Technologies, Inc., Santa Clara, CA, USA). Reverse transcription was performed with a 20 ng sample of RNA, which was incubated for 60 min at 42°C followed by 5 min at 95°C. Following synthesis, the cDNA template was diluted 80-fold with nuclease-free H₂O. Then qPCR was performed as follows: Denaturation at 95°C for 10 min, followed by 40 amplification cycles of 95°C for 10 sec and 60°C for 1 min (ramp-rate, 1.6°C/sec). All samples were normalized to the U6 expression level using the 2^{-ΔΔC_q} method (16).

Plasmid construction. DRAM1 was identified as a potential target of miR-26b with TargetScan (<http://www.targetscan.org/>), which was used to identify autophagy-associated genes. The wild-type (WT) 3'-untranslated region (3'UTR) of DRAM1, including the putative miR-26b-binding site, was extracted by performing PCR with genomic DNA obtained from the extracted blood of a healthy

human donor. DNA was extracted using Rapid DNA extraction and detection kit (Tiangen Biotech Co., Ltd., Beijing, China). The amplified product was then cloned into the *Hind*III and *Xho*I sites of the pMIR vector (Promega Corporation, Madison, WI, USA). PCR was also performed to generate a DRAM1 3'UTR with a mutated miR-26b binding site. The primer sequences were WT forwards, 5'-GTCAAGCTTCTG CAGCACATCCAGGACTTGAATTTTCATTACGAGTTCC T-3', WT reverse, 5'-CCACTCGAGACCAGGCGATACAGA CTATT-3'; mutant forwards, 5'-GTCAAGCTTCTG CAGC ACATCCAGGACAACAATTTTCATTACGAGTTCCCT-3', mutant reverse, 5'-CCACTCGAGACCAGGCGATACAGA CTATT-3'. PCR was performed as follows: Denaturation at 95°C for 5 min, 40 amplification cycles of 95°C for 10 sec, 55°C for 15 sec and 72°C for 90 sec, followed by 72°C for 5 min (ramp-rate, 1.6°C/sec). PrimeSTAR® Max DNA Polymerase (R045Q; Takara Biotechnology Co., Ltd., Dalian, China) was used for PCR amplification. DNA sequencing was used to verify the identities of the PCR products incorporated into the plasmids.

Luciferase reporter assays. MCF7 cells were cultured in 96-well plates (5x10⁴ cells/well). Lipofectamine® 2000 was used to transfect the cells with 200 ng of pMIR-DRAM1 3'UTR and 5 ng of the pRL-SV40 vector containing the *Renilla* luciferase gene used to normalize transfection efficiency (Promega Corporation), in addition to 100 nmol of the miR-26b mimic or NC. At 48 h after transfection, the Dual-Luciferase Reporter assay (Promega Corporation) was used to examine firefly and *Renilla* luciferase activities. Each transfection was repeated 5 times in three independent experiments.

Western blot analysis. MCF7 cells were irradiated for 24 h (a time selected based on a time-course curve) and harvested; 1 ml lysis buffer (50 mM NaCl, 10 mM HEPES, 1 mM EDTA, 1 mM DTT, 1% NP-40, 0.1% SDS and 1 mM PMSF) and 10 μl protease inhibitor cocktail (P8340; Sigma-Aldrich; Merck KGaA) was added to the cell pellets. Subsequently, protein was quantified using BCA Protein Assay kit (P0012S; Beyotime Institute of Biotechnology, Haimen, China). SDS-PAGE was used to separate 60 μg of total cellular protein extract; the separated bands were transferred onto a nitrocellulose membrane for western blotting. Membranes were blocked with 5% skimmed milk in Tris-Buffered Saline Tween-20 for 1 h at room temperature. Subsequently, horseradish peroxidase-conjugated secondary antibodies [HRP-Goat anti-Rabbit IgG (cat no. bs-0295G-HRP) and HRP-Goat anti-Mouse IgG (cat no. bs-0296G-HRP; both 1:2,000); Boster Biological Technology, Pleasanton, CA, USA] was added for 1 h at room temperature. Primary antibodies were used against DRAM1 (1:300; ab72171; Abcam; Cambridge, UK), light chain 3 (LC3) I and II (1:300; 4108S; Cell Signaling Technology; Danvers, MA, USA), and GAPDH (1:1,000; sc-32233; Santa Cruz Biotechnology, Inc.). Immunoreactive bands were detected by chemiluminescence (sc-2048; Santa Cruz Biotechnology, Inc.). The staining intensities of individual proteins were measured using ImageJ software (version 1.41; National Institutes of Health, Bethesda, MD, USA), and expressed relatively to the intensity of the GAPDH band.

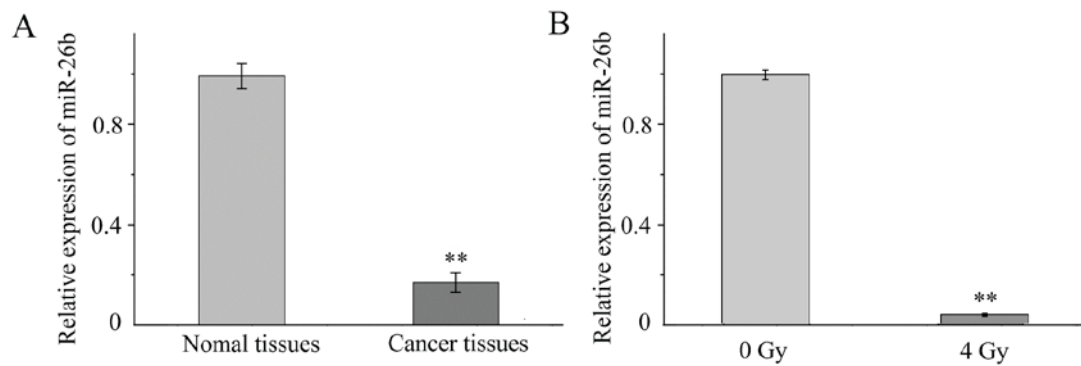


Figure 1. miR-26b relative expression was decreased expression in cancer tissue and irradiated MCF7 cells. Reverse transcription-quantitative polymerase chain reaction was used to quantify the level of miR-26b in tissue samples and cells. (A) Level of miR-26b in breast cancer tissue compared with adjacent noncancerous tissue. (B) Level of miR-26b expression in MCF7 cells exposed to 4 Gy of radiation compared with MCF7 control cells. ** $P < 0.01$. miR, microRNA.

Monodansylcadaverine (MDC) staining assay. MCF7 cells (4×10^5 cells/well) were seeded in 60-mm cell culture dishes and let sit overnight at room temperature. Each group of cells received the specified dose of IR. After 24 h, they were washed twice in cold PBS solution. The cells were incubated in DMEM containing 50 mM MDC for 1 h at 37°C to label the autophagic vacuoles; they were then washed with PBS and fixed by a 15 min immersion in 4% paraformaldehyde solution at room temperature. The cells were analyzed for fluorescence with a FACSsort Flow Cytometer (BD Biosciences, Franklin Lakes, NJ, USA). Data were analyzed using Cell Quest software (version 5.1; BD Biosciences) and FlowJo software (version 7.6.5; Tree Star Inc., Ashland, OR, USA).

Statistical analysis. The Student's t test and the χ^2 test were used to analyze experimental data, and data are presented as the mean \pm standard deviation using SPSS software (version 12.0; SPSS, Inc., Chicago, IL, USA). $P < 0.05$ was considered to indicate a statistically significant difference.

Results

miR-26b expression is reduced in breast cancer tissue and irradiated MCF7 cells. RT-qPCR was performed to investigate the expression of miR-26b in tissue samples and MCF7 cells. It was demonstrated that the expression of miR-26b was significantly lower in the three samples of breast cancer tissue when compared with expression in the noncancerous adjacent tissue ($P < 0.001$; Fig. 1A). In addition, miR-26b expression was significantly downregulated in MCF7 cells exposed to 4-Gy IR compared with MCF7 cells that were not irradiated ($P < 0.01$; Fig. 1B).

miR-26b may regulate IR-induced autophagy in MCF7 cells. The effect of miR-26b on autophagy in MCF7 cells was examined by performing a western blot analysis for LC3II protein expression. Cells exposed to IR exhibited an increased level of LC3II protein expression, which was suppressed following transfection with an miR-26b mimic. Furthermore, LC3II protein was overexpressed in cells treated with the miR-26b inhibitor ($P < 0.01$; Fig. 2A). MDC staining demonstrated that exposure to IR increased the rate of autophagy by 21.88% in the control cells, by 16.80% in

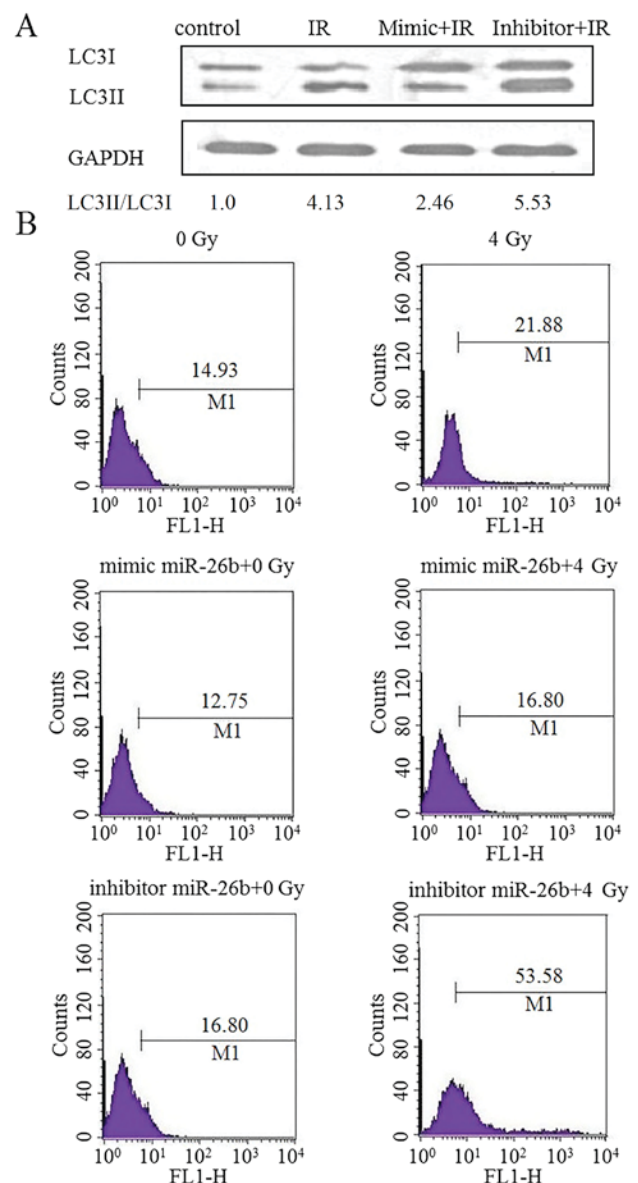


Figure 2. miR-26b regulated autophagy in MCF7 cells exposed to IR. MCF7 cells that were transfected with NC, miR-26b mimic or the miR-26b inhibitor were subsequently exposed to IR. (A) miR-26b promoted the LC3II protein expression induced by IR. (B) MCF7 cells were exposed to 4 Gy of IR. Staining with monodansylcadaverine was detected by flow cytometry at 24 h. miR, microRNA; IR, ionizing radiation; IR, ionizing radiation; NC, negative control; LC3II, light chain 3-II.

Discussion

miRNAs are differentially expressed in normal tissue compared with cancer tissue; there may be a critical role for dysregulated miRNA expression in tumorigenesis (17-20). However, the mechanisms by which miRNAs regulate autophagy are only starting to be explored. A number of miRNAs have been demonstrated to modulate autophagy in human cancer cells by targeting autophagy-associated genes (21-23). These studies have enriched the understanding of the autophagy signaling process and provided novel therapeutic perspectives. A range of previous studies have investigated the role that microRNAs serve in the cellular response to radiation therapy by examining the process of autophagy (16,24-29).

The downregulation of miR-26b expression in breast cancer tissue compared with noncancerous tissue was previously identified, as well as in breast cancer cells compared with normal breast cells (10). In the present study, upregulated miR-26b expression levels were associated with a reduction in the levels of IR-induced autophagy in MCF7 cells. Additionally, DRAM1 mRNA was identified as a potential target for miR-26b. Previous studies have demonstrated that the DRAM1 gene codes for a number of splice variant proteins that are induced by p53, and that these proteins localize to autophagosomes and peroxisomes, where they may be required for the process of p53-induced autophagy (30,31). The luciferase and western blot assays of the present study identified DRAM1 as a target of miR-26b. MCF7 cells transfected with an miR-26b mimic exhibited the reduced expression of DRAM1, which may be due to the 3'UTR of the DRAM1 mRNA being targeted. Additionally, transfection with the miR-26b mimic suppressed the expression of DRAM1 protein in MCF7 cells, regardless of whether they had been exposed to IR. When taken together, the data suggest that miR-26b, at least partially, inhibits IR-induced autophagy in MCF7 cancer cells by inhibiting DRAM1. Overall, the results of the present study may improve the understanding of the various mechanisms by which miRNAs influence cells.

It was also demonstrated that IR downregulated miR-26b expression in MCF7 cells. MCF7 cells transfected with an miR-26b inhibitor exhibited reduced miR-26b expression prior to IR and enhanced miR-21b expression following IR; however, the underlying mechanism for this response remains unclear. Previous studies have demonstrated that miRNA modulation may allow an improvement of the clinical effect of radio- or chemotherapy (32-34). However, the mechanisms by which miRNAs produce their effects are not fully understood. Additional studies are required to identify the miRNAs that modulate the effects of chemo- or radiotherapy, as well as their effect on cellular metabolic processes. It will also be necessary to confirm that patients can be safely and effectively treated by a clinical regimen that targets miRNAs.

In summary, it was demonstrated that miR-26b may regulate the basal level of autophagy in MCF7 cells, as well as autophagy resulting from IR exposure. DRAM1 was identified as a target gene through which miR-26b may modulate autophagy. The present study may provide evidence of a specific role for miR-26b in carcinogenesis and cancer therapy effectiveness. This result may enhance the understanding of the miRNA-modulated networks associated with autophagy,

ultimately facilitating improvement of the methods for treating cancer.

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