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ORIGINAL ARTICLE

Downregulated lncRNA *DRAIC* enhances the radiotherapy sensitivity of human HCC cell line *HepG2* by targeting *miR-223-3p*

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Abstract

Objective This study aims to investigate the effects of the long noncoding RNA (lncRNA) *DRAIC* on the proliferation, apoptosis, and radiosensitivity of hepatocellular carcinoma (HCC) cells and the molecular mechanisms involved.

Methods Cancer tissues and their corresponding adjacent tissues from 30 patients with HCC were collected, and the expression levels of *DRAIC* and *miR-223-3p* were detected via RT-qPCR. *DRAIC* interference and *miR-223-3p* overexpression vectors were transfected into *HepG2* cells. In addition, *DRAIC* and *miR-223-3p* interference vectors were co-transfected into *HepG2* cells. The constructed cells were irradiated at 4 Gy. Cell colony formation assay, MTT assay, and flow cytometry were performed to detect the radiosensitivity, proliferation inhibition rate, and apoptosis rate of *HepG2* cells, respectively. Dual luciferase reporter gene assay was performed to detect the targeted regulation of *DRAIC* on *miR-223-3p* expression.

Results The expression level of *DRAIC* in HCC tissues was higher than that in paracancer tissues, whereas the expression level of *miR-223-3p* was lower in HCC tissues than that in paracancer tissues ($P < 0.05$). Inhibition of *DRAIC* expression or overexpression of *miR-223-3p* increased the proliferation inhibition and apoptosis rates of *HepG2* cells ($P < 0.05$). After irradiation, cell survival fraction decreased and cell proliferation inhibition and apoptosis rates increased ($P < 0.05$). *DRAIC* targeted the regulation of *miR-223-3p* expression, and interference of *miR-223-3p* expression reversed the effects of inhibiting *DRAIC* expression on the proliferation, apoptosis, and radiosensitivity of *HepG2* cells.

Conclusion Inhibition of *DRAIC* expression can inhibit the proliferation of *HepG2* cells, promote cell apoptosis, and enhance the radiosensitivity of cells via upregulation of *miR-223-3p*.

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Key words: the long noncoding RNA (lncRNA) *DRAIC*; *miR-223-3p*; hepatocellular carcinoma (HCC); radiosensitivity medium classification

Hepatocellular carcinoma (HCC) is a common malignant tumor in China, and is often treated with surgery and chemotherapy [1]. With the popularization and development of precision radiotherapy in recent years, radiotherapy has become an effective means to treat liver cancer [2]. However, the resistance of HCC cells to radiotherapy reduces the sensitivity and limits the wide application of radiotherapy. Finding biomarkers that are predictive of neoadjuvant therapy and have a prognostic effect on the overall survival is a research hotspot in the field of neoadjuvant therapy. Long noncoding RNAs (lncRNAs) are transcripts of more than 200 nucleotides and are closely associated with various diseases, including cancer. LncRNAs are considered potential biomarkers for cancer diagnosis, specifically as tumor promoters or suppressors [3]. Studies have reported that the lncRNA *DRAIC* is upregulated in gastric cancer tissues and cell lines, which can be used as an indicator of poor prognosis in patients with gastric cancer. Inhibition of *DRAIC* can inhibit the proliferation, migration, and invasion of gastric cancer cells [4]. The lncRNA *DRAIC* regulates the DNA damage response of nasopharyngeal carcinoma cells to achieve radiation resistance [5]. However, its role in HCC and whether it affects the radiosensitivity of HCC

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cells remain unclear. *DRAIC* has been reported to have binding sites for *miR-223-3p*. Overexpression of *miR-223-3p* can inhibit the proliferation and migration of HCC cells [6]. Therefore, this experiment was conducted to investigate the effects of the lncRNA *DRAIC* on the proliferation, apoptosis, and radiosensitivity of HCC cells and whether the mechanism was related to *miR-223-3p*.

Materials and methods

Specimens

Thirty patients with HCC with complete clinicopathological data were admitted to our hospital (PLA Rocket Force Characteristic Medical Center, Beijing, China) from June 2015 to June 2020. All patients were checked through pathological examination, and their cancer and paracancer tissues were surgically removed. In addition, all patients signed informed consent forms. This experiment was reviewed and approved by the Ethics Committee of our hospital.

Cells and reagents

Human HCC cell line, *HepG2*, was purchased from Shanghai Cell Bank (Chinese Academy of Sciences, China). The main reagents were as follows: RPMI-1640 complete medium was purchased from Gibco (San Diego, California, USA); Fluorescence quantitative PCR kit (Dingguochangsheng, Beijing, China); methyl thiazolyl tetrazolium (MTT) kit (Tongwei, LTD, Shanghai, China). The apoptosis detection kit (Emijie, Wuhan, China), protein lysate (Yuanye, Shanghai, China), double luciferase reporter gene detection kit (Biyuntian, Shanghai, China). The rabbit polyclonal antibodies cyclin D1 (AB39570), Bcl-2 (AB25644) and rabbit monoclonal antibodies p21 (AB13662), Bax (AB25436), and cleaved caspase-3 (AB66254) were purchased from Abcam (Boston, Massachusetts, USA).

Experimental grouping

HepG2 cells were cultured in RPMI-1640 complete medium. *DRAIC* interference expression vector and a negative control and *miR-223-3p* mimics and a negative control were transfected into *HepG2* cells at the logarithmic growth stage. They were classified as short interfering (si)-*DRAIC*, *si*-NC, *miR-223-3p*, and *miR*-NC groups, respectively. The *DRAIC* interference expression vector was co-transfected with *miR-223-3p* inhibitor or a negative control into *HepG2* cells and was classified as *si-DRAIC* + anti-*miR-223-3p* and *si-DRAIC* + anti-*miR*-NC groups, respectively. Cells in the *si*-NC, *si-DRAIC*, *miR*-NC, *miR-223-3p*, *si-DRAIC* + anti-*miR*-NC, and *si-DRAIC* + anti-*miR-223-3p* groups were irradiated with 4 Gy radiation and were recorded as 4 Gy + *si*-NC, 4 Gy + *si*-DRAIC, 4 Gy + *miR*-NC, 4 Gy + *miR-223-3*, 4 Gy + *si-DRAIC* + anti-*miR*-NC, and 4 Gy + *si-DRAIC* + anti-*miR-223-3p* groups, respectively.

Real-time quantitative PCR (RT-qPCR) detection

RNA was extracted from tissues and cells. Next, RT-qPCR was performed according to the kit instructions, with GAPDH and U6 as internal controls, and the relative expression level was calculated via the $2^{-\Delta\Delta Ct}$ method. The following primers were used: *DRAIC* upstream primer sequence: 5'-CTGCCTCCACCCGTGTACCG-3' and downstream primer sequence: 5'-ATCGGCGTGGGTGTCTCACC-3'; GAPDH upstream primer sequence: 5'-TGGTCr-CCCAAGCGTCGATag-3' and downstream primer sequence: 5'-AGCTTGGACGAGATCGGGGAA-3'; *miR-223-3p* upstream primer sequence: 5'-AcACTT-ATCGGTAGTGTGGTC-3' and downstream primer sequence: 5'-AGCTCGTCTCTCCCGTCCCT-3'; U6 upstream primer sequence: 5'-CCAACGA-AACCGTCGCATCCAGT-3' and downstream primer sequence: 5'-AgGAAAAGTTCACAatCTCGA-3'.

Cell colony formation assay

Cells of the *si*-NC, *si-DRAIC*, *miR*-NC, *miR-223-3p*, *si-DRAIC* + anti-*miR*-NC, and *si-DRAIC* + anti-*miR-223-3p* groups were inoculated in a 60 mm petri dish and irradiated with 0, 2, 4, 6 and 8 Gy radiation. After irradiation, the cultures were continued for two weeks. The cells were subjected to Giemsa staining, and colonies of more than 50 cells were counted under an optical microscope (BX53, Olympus, Japan). GraphPad Prism 5 (National Institutes of Health) was used to fit the cell survival curve.

MTT assay

The cells were cultured for 48 h, MTT assay was performed according to the manufacturer's instructions, and MTT solution and dimethyl sulfoxide were added. The absorbance (*A*) value at 490 nm was detected using a microplate reader (Multiskan FC, Thermo). The proliferation inhibition rate was calculated using the following formula: [1 – *A* (experimental group)] / *A* (blank group) × 100%.

Flow cytometry

HepG2 cells were digested with 0.25% trypsin and centrifuged. Flow buffer was then added to the cells according to the manufacturer's instructions, and the cells were resuspended (Phosphate buffer). Next, 5 μL annexin V-APC was added and the cells were incubated for 30 min, and then 5 μL PI was added.

Western blot

The cells were collected (1×10^6 cells/mL) and subjected to total protein extraction. The proteins (100 μg) were then denatured, separated via SDS-PAGE, transferred to the PVDF membrane, and then sealed for 1 h. They were incubated with the primary antibody (diluted 1:500) overnight at 4 °C and with the secondary antibody for 1 h. ECL developing solution A and the same volume of liquid B was dropped onto the PVDF membrane, and an image was captured using the AI600 imaging system. The absorbance value was analyzed using Image J software (Ver. 1.48, Bethesda, MD, USA) and was compared with β-actin as the internal control.

Double luciferase reporter gene assay

The wild-type *DRAIC* sequence containing the predicted *miR-223-3p* binding site or mutants at each site was cloned into the PsichecK-2 plasmid and named *DRAIC*-WT or *DRAIC*-MUT reporter gene. The luciferase reporter gene was transfected into *HepG2* cells with *miR-223-3p*, anti-*miR-223-3p*, or the corresponding controls. After 48 h, luciferase activity was measured using the dual luciferase reporter gene assay system (Promega).

Statistical analysis

SPSS 20.0 software was used for statistical analysis. The measurement data consistent with normal distribution were expressed as mean ± standard deviation ($X \pm S$). *T*-test and LSD-*T* test were performed for comparison between two groups, and one-way ANOVA was used for comparison between multiple groups. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Expression of lncRNA *DRAIC* and *miR-223-3p* in HCC tissues

DRAIC expression level in HCC tissues was higher than that in paracancer tissues, whereas the *miR-223-3p* expression level in HCC tissues was lower than that in paracancer tissues ($P < 0.05$; Fig. 1).

Effect of inhibiting lncRNA *DRAIC* expression on the radiosensitivity of *HepG2* cells

The cell survival fraction of the *si-DRAIC* group decreased after irradiation at different doses ($P < 0.05$), and the radiosensitization ratio was 1.725 (Fig. 2).

Effects of inhibition of lncRNA *DRAIC* expression combined with 4 Gy radiation on the proliferation and apoptosis of *HepG2* cells

The proliferation inhibition and apoptosis rates of *HepG2* cells in the *si-DRAIC* group were higher than those in the *si*-NC group. The expression levels of cyclin D1 and Bcl-2 in the *si-DRAIC* group were lower than those in the *si*-NC group, whereas the expression levels of p21, Bax, and cleaved caspase-3 in the *si-DRAIC* group were higher than those in the *si*-NC group ($P < 0.05$). Furthermore, the proliferation inhibition and apoptosis rates of cells in the 4 Gy + *si-DRAIC* group were higher than those in 4 Gy + *si*-NC group. The expression levels of cyclin D1 and Bcl-2 in the 4 Gy + *si-DRAIC* group were lower than those in 4 Gy + *si*-NC group, whereas the expression levels of p21, Bax, and cleaved caspase-3 in the 4 Gy + *si-DRAIC* group were higher than those in the 4 Gy + *si*-NC group ($P < 0.05$; Fig. 3).

LncRNA *DRAIC* targeted regulation of *miR-223-3p* expression

starBase prediction showed that the lncRNA *DRAIC* contained binding sites for *miR-223-3p* (Fig. 4a). The luciferase activity of *HepG2* cells co-transfected with WT-*DRAIC* and *miR-223-3p* was lower than that of cells co-transfected with WT-*DRAIC* and *miR*-NC ($P < 0.05$; Fig. 4b). Overexpression of *DRAIC* decreased *miR-223-3p* expression levels, inhibited *DRAIC* expression, and increased *miR-223-3p* expression levels ($P < 0.05$; Fig. 4c). The *DRAIC* expression level was negatively correlated with *miR-223-3p* expression level in tumor and fat cancer tissues ($r = -0.528$, $P < 0.001$; Fig. 4d).

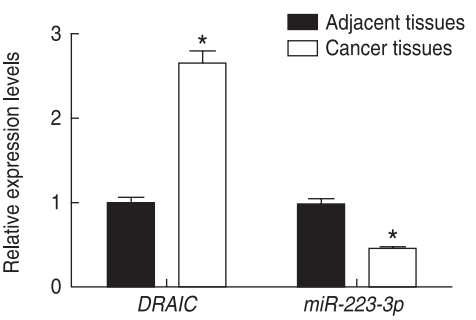

Fig. 1 Expression of lncRNA *DRAIC* and *miR-223-3p* in HCC tissues. * $P < 0.05$ compared with adjacent tissues

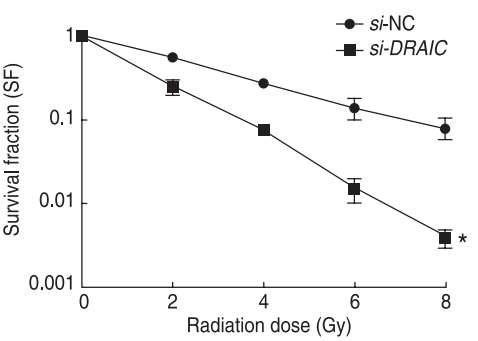

Fig. 2 Effect of inhibition of lncRNA *DRAIC* expression on *HepG2* cell survival score. * $P < 0.05$ compared with *si*-NC group

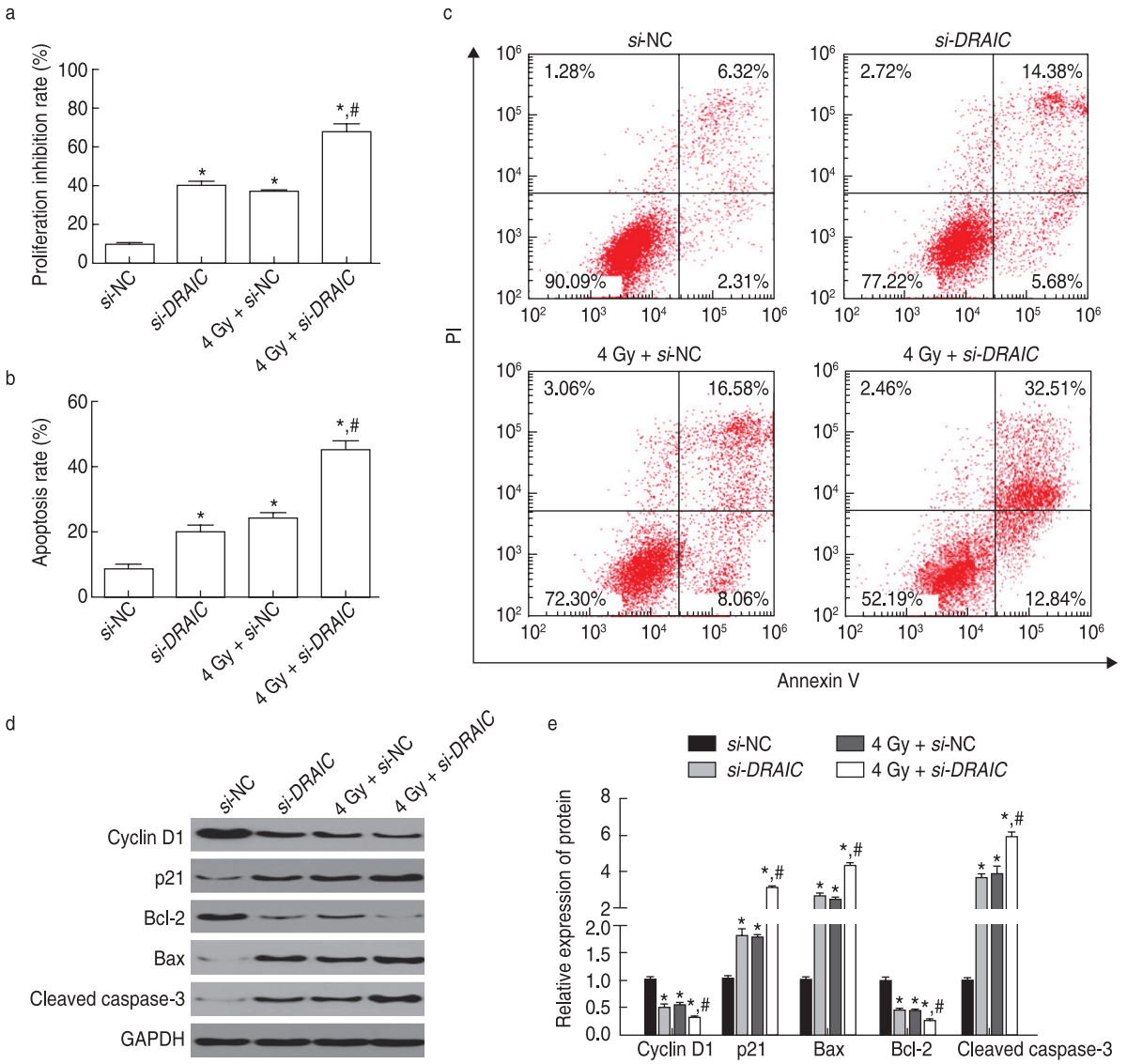

Fig. 3 Effects of inhibition of lncRNA *DRAIC* expression combined with 4 Gy radiation on the proliferation and apoptosis of *HepG2* cells. (a) Proliferation inhibition rate; (b) Apoptosis rate; (c) Apoptosis was detected via flow cytometry; (d) Western blotting was performed to detect protein expression; (e) Relative expression of proteins. * $P < 0.05$ compared with *si*-NC group; # $P < 0.05$ compared with 4 Gy + *si*-NC group

Effect of *miR-223-3p* overexpression on the radiosensitivity of *HepG2* cells

The cell survival score of the *miR-223-3p* group decreased after irradiation at different doses ($P < 0.05$). The radiosensitization ratio of cells was 1.701 (Fig. 5).

Effects of *miR-223-3p* overexpression combined with 4 Gy irradiation on the proliferation and apoptosis of *HepG2* cells

The proliferation inhibition and apoptosis rates of *miR-223-3p* group cells were higher than those of *miR*-NC group cells. The expression levels of cyclin D1 and Bcl-2 in the *miR-223-3p* group were lower than those in the *miR*-NC group, whereas the expression levels of p21, Bax, and cleaved caspase-3 in the *miR-223-3p* group were higher than those in the *miR*-NC group ($P < 0.05$). Furthermore, the proliferation inhibition and apoptosis rates of cells in the 4 Gy + *miR-223-3p* group were higher than those in 4 Gy + *miR*-NC *group*. The expression levels of cyclin D1 and Bcl-2 in the 4 Gy + *miR-223-3p* group were lower than those in 4 Gy + *miR*-NC group, whereas the expression levels of p21, Bax, and cleaved caspase-3 in the 4 Gy + *miR-223-3p* group were higher than those in the 4 Gy + *miR*-NC group ($P < 0.05$; Fig. 6).

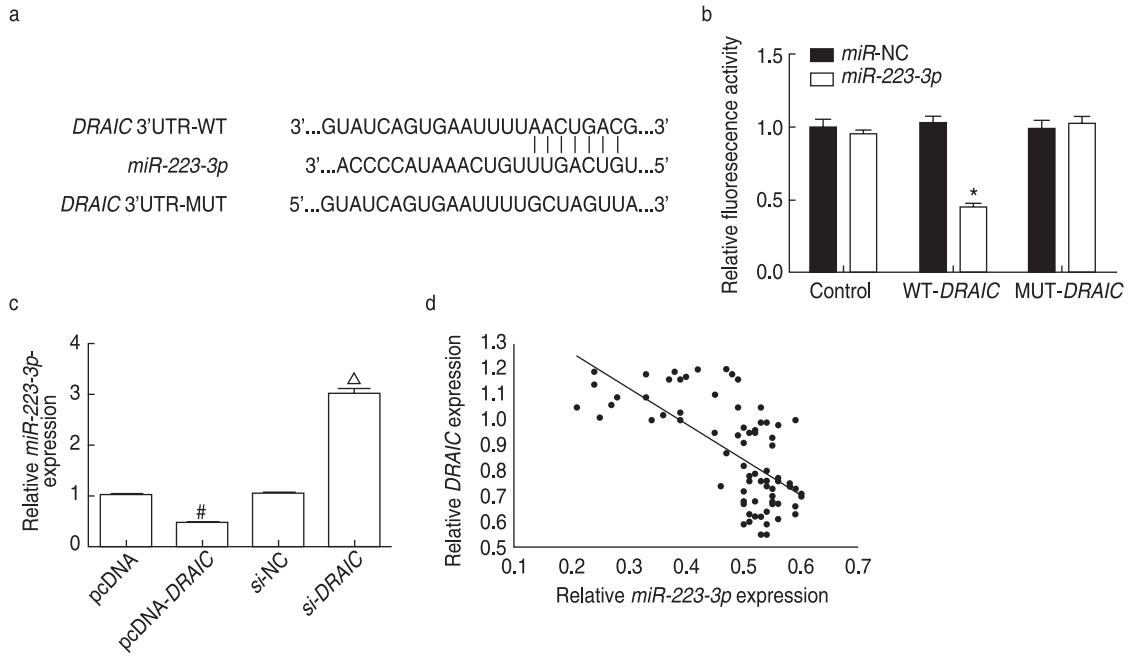

Fig. 4 LncRNA *DRAIC* targeting regulated the expression of *miR-223-3p*. (a) Schematic of lncRNA *DRAIC* and *miR-223-3p* binding; (b) luciferase reporter gene assay verified that *miR-223-3p* was the target of the lncRNA *DRAIC*; (c) lncRNA *DRAIC* was detected to affect endogenous *miR-223-3p* levels via RT-qPCR; (d) Pearson linear analysis of the correlation between lncRNA *DRAIC* and *miR-223-3p* in lung cancer tissues. * $P < 0.05$ compared with *miR*-NC group; # $P < 0.05$ compared with pcDNA group; △ $P < 0.05$ compared with *si*-NC group

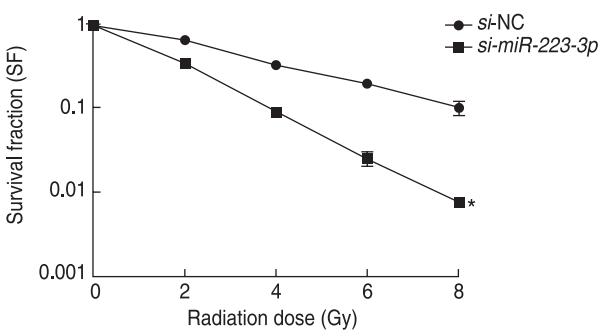

Fig. 5 Effect of *miR-223-3p* overexpression on the survival score of *HepG2* cells. * $P < 0.05$ compared with *miR*-NC

Interference with *miR-223-3p* expression reversed the effect of inhibiting *DRAIC* expression on the radiosensitivity of HCC *HepG2* cells

After irradiation at different doses, the cell survival score of the *si-DRAIC* + anti-*miR*-NC group was lower than that of the *si*-NC group, and the radiosensitization ratio was 1.745. In contrast, the cell survival score of the *si-DRAIC* + anti-*miR-223-3p* group was higher than that of the *si-DRAIC* + anti-*miR*-NC group, and the radiosensitization ratio was 1.140. Furthermore, the proliferation inhibition and apoptosis rates of cells in the 4 Gy + *si-DRAIC* + anti-*miR-223-3p* group were lower than those in the 4 Gy + *si-DRAIC* + anti-*miR*-NC group. The expression levels of cyclin D1, Bcl-2, and caspase-3 in the 4 Gy + *si-DRAIC* + anti-*miR-223-3p* group were higher than those in the 4 Gy + *si-DRAIC* + anti-*miR*-NC group, whereas the expression levels of p21, Bax, and cleaved caspase-3 in the 4 Gy + *si-DRAIC* + anti-*miR-223-3p* group were lower than those in the 4 Gy + *si-DRAIC* + anti-*miR*-NC group ($P < 0.05$; Fig. 7 and 8).

Discussion

HCC is a common malignant tumor in China, with a high degree of malignancy, recurrence, and mortality. The treatment methods mainly include surgery, chemotherapy, and radiotherapy. However, the resistance of HCC cells to radiotherapy limits its efficacy; thus, improving the radiotherapy sensitivity of HCC cells has important clinical significance for the treatment of HCC. LncRNAs usually regulate gene expression, including the transcriptional or post-transcriptional regulation of oncogenes and tumor suppressor genes. The lncRNA *DRAIC* is a novel lncRNA located at the 15Q23 position of the human chromosome, which has been recently reported to play an important role in the regulation of cancer occurrence and development. Saha *et al* [4] found that the lncRNA *DRAIC* inhibits the activation of the NF-κB pathway through interacting with the inhibitors

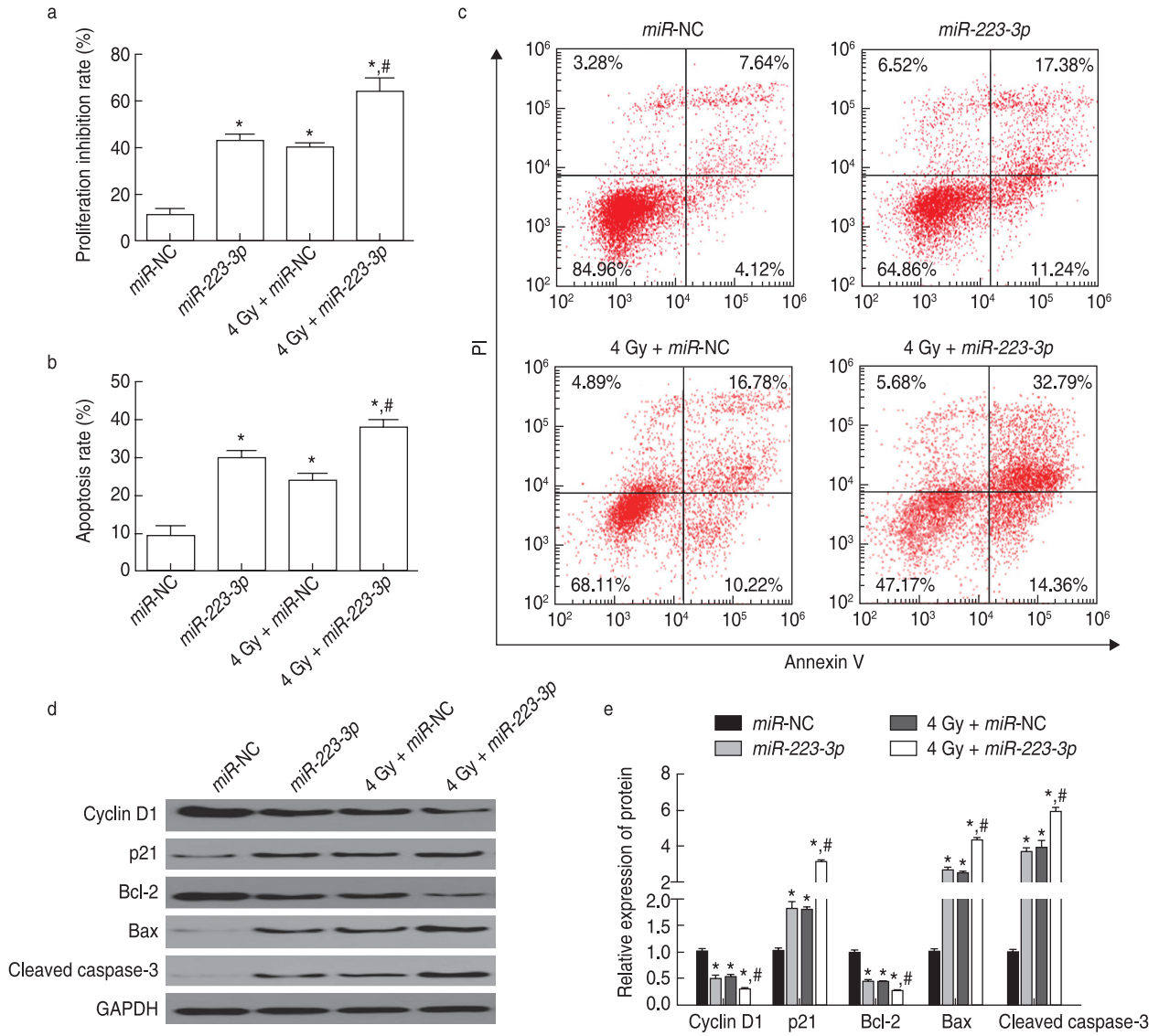

Fig. 6 Effects of inhibition of *miR-223-3p* expression combined with 4 Gy radiation on the proliferation and apoptosis of *HepG2* cells. (a) Proliferation inhibition rate; (b) apoptosis rate; (c) apoptosis was detected via flow cytometry; (d) Western blotting was performed to detect protein expression; (e) relative expression of proteins. * $P < 0.05$ compared with *miR*-NC group; # $P < 0.05$ compared with 4 Gy + *miR*-NC group

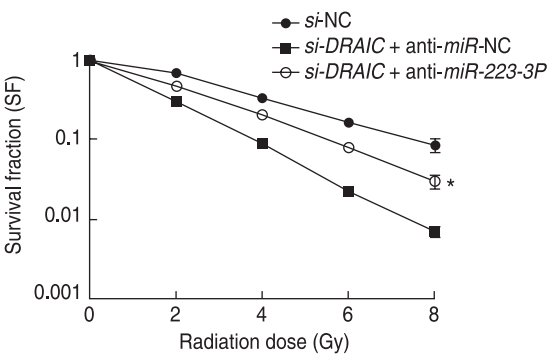

Fig. 7 Interference with *miR-223-3p* expression reversed the effect of inhibition of *DRAIC* expression on the survival scores of *HepG2* cells. * $P < 0.05$ compared with *si-DRAIC* + anti-*miR*-NC group

of IκB kinase β, thereby inhibiting the proliferation and invasion of prostate cancer cells, growth of xenograft tumors, and progression of prostate cancer.

Deng *et al* [7] found that the lncRNA *DRAIC* regulates the expression of *miR-223-3p*, and the inhibited expression can inhibit the migration and invasion of gastric cancer cells and promote their apoptosis. Li *et al* [8] found that *DRAIC* is highly expressed in esophageal cancer tissues and cells, and interference with *DRAIC* expression can inhibit the proliferation and autophagy of liver cancer cells. Although TCGA and RNA sequencing data have indicated that the lncRNA *DRAIC* is upregulated in HCC cells, its mechanism in HCC development has not been clarified. In this study, the expression of *DRAIC*

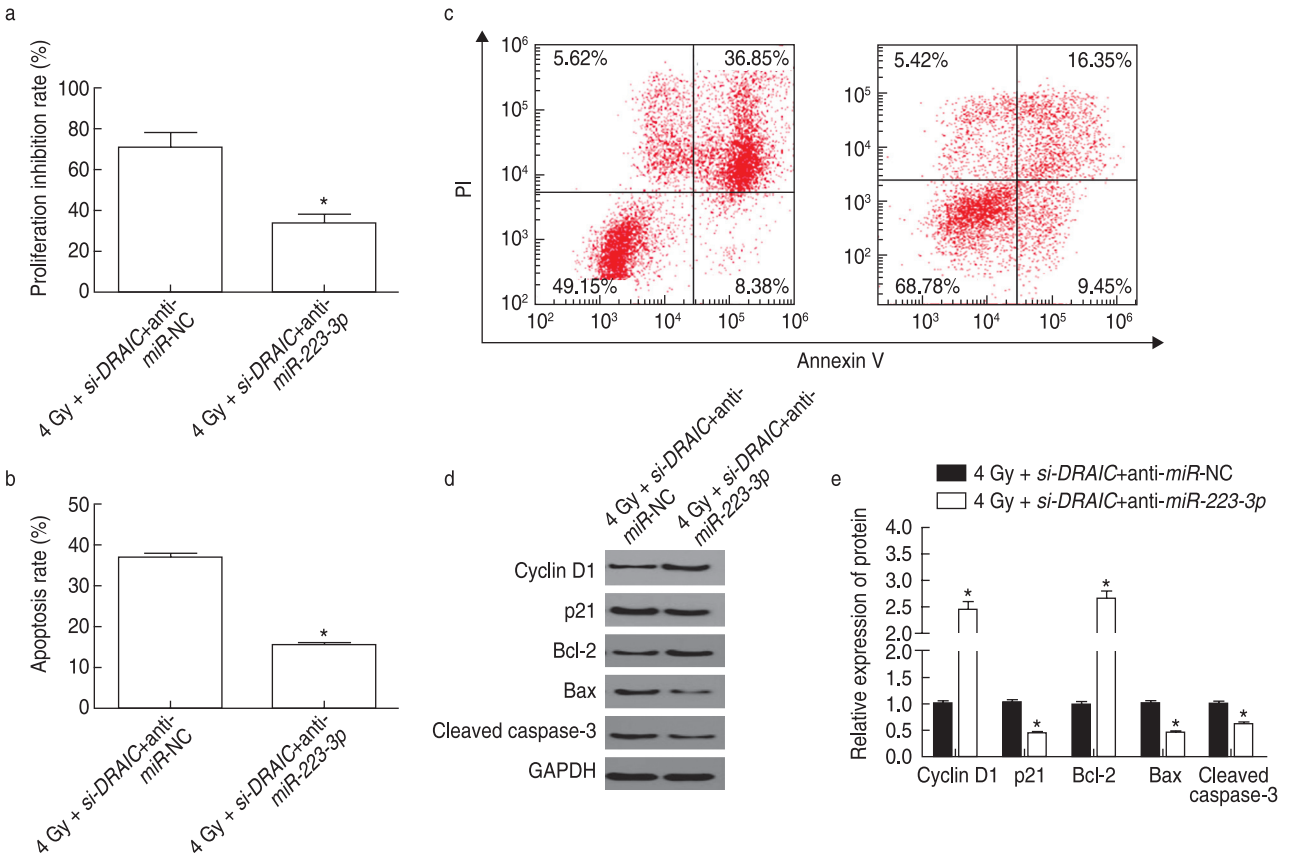

Fig. 8 Interference with *miR-223-3p* expression reversed the effects of inhibition of *DRAIC* expression combined with 4 Gy irradiation on the proliferation and apoptosis of *HepG2* cells. (a) Proliferation inhibition rate; (b) apoptosis rate; (c) apoptosis was detected via flow cytometry; (d) Western blotting was performed to detect protein expression; (e) relative expression of proteins. * $P < 0.05$ compared with 4 Gy + *si-DRAIC* + anti-*miR*-NC group

in HCC tissues was significantly higher than that in the adjacent tissues ($P < 0.05$). After transfection with *DRAIC* interference expression vector, the cell proliferation inhibition and apoptosis rates increased. These results indicated that inhibition of *DRAIC* could inhibit the proliferation and apoptosis of *HepG2* cells. The cells transfected with *DRAIC* interference expression vector were irradiated at different doses. The results showed that the survival fraction of cells decreased, indicating that inhibition of *DRAIC* expression increased the sensitivity of cancer cells to radiation. In addition, the proliferation inhibition and apoptosis rates of *HepG2* cells were significantly increased after transfection with *DRAIC* interference expression vector combined with 4 Gy radiation, indicating that the combination of inhibition of *DRAIC* expression and irradiation had a stronger tumor inhibition effect on *HepG2* cells than interference alone.

Bioinformatic analysis of the lncRNA *DRAIC* was performed to identify and verify *miR-223-3p* as a binding target. The *miR-223-3p* presents low expression in a variety of cancers, and its overexpression can inhibit the proliferation and migration of a variety of cancer cells [9–10]. Xu *et al* [11] found that the expression of *miR-223-3p* was reduced in HCC cells, and *miR-223-3p* can inhibit the proliferation, migration, invasion, and other malignant phenotypes of HCC cells through targeting the adipocyte atypical cadherin 1. Wang *et al* [12] showed that *miR-223-3p* is underexpressed in breast cancer tissues and its overexpression can inhibit the expression of an oncogene in epithelial cell transformation sequence 2, thus inhibiting the invasion and migration of breast cancer cells and promoting cell apoptosis. Sun *et al* [13] also found that the expression of *miR-223-3p* was decreased in oral squamous cell carcinoma tissues and cell lines, and its overexpression inhibited the proliferation, migration, and invasion of oral squamous cell carcinoma cells and induced cell apoptosis. The results of this study showed that the expression level of *miR-223-3p* in HCC tissues was decreased, which was consistent with the results of previous studies, suggesting that *miR-223-3p* plays a tumor suppressive role in HCC. Dong *et al* [14] demonstrated that *miR-223-3p* was downregulated in HCC cell lines, and *miR-223-3p* overexpression inhibited cell proliferation and migration and increased cisplatin sensitivity. The results of this study also showed that *miR-223-3p* overexpression alone or combined with irradiation

increased the proliferation inhibition and apoptosis rates of *HepG2* cells, and the cell survival fraction decreased after irradiation at different doses. These results indicated that the overexpression of *miR-223-3p* could inhibit the proliferation of *HepG2* cells, promote apoptosis, and increase the radiosensitivity of cells. This study also found that the lncRNA *DRAIC* regulated and interfered with *miR-223-3p* expression, which reversed the effects of inhibiting *DRAIC* expression on *HepG2* cell proliferation, apoptosis, and radiosensitivity.

In conclusion, inhibition of the lncRNA *DRAIC* expression can inhibit the proliferation of *HepG2* cells, promote apoptosis, and enhance the radiosensitivity of cells, and the mechanism may be related to *miR-223-3p*.

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Conflicts of interest
The authors indicated no potential conflicts of interest.

Author contributions
All authors contributed to data acquisition, data interpretation, and reviewed and approved the final version of this manuscript.

Data availability statement
Not applicable.

Ethical approval
Not applicable.

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