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Radiosensitizing effect of deferoxamine on human glioma cells

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► ***Original article***

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ABSTRACT

Background*:** Tumor cells exhibit an increased requirement for iron to support their rapid proliferation. Deferoxamine (DFO), an iron chelator, has been reported to have anti-proliferative effects on cancer cells through induction of apoptosis and cell cycle arrest. X-rays also induce apoptosis and cell cycle arrest. However, limited information is available regarding the effect of iron depletion on radiotherapy. In this study, the radiosensitizing effect of DFO was investigated in human glioma U251 cells. ***Materials and Methods*:** U251 cells were pretreated with DFO before exposure to X-rays. The radiosensitizing effect of DFO on U251 cells was evaluated with a clonogenic formation assay. Apoptosis and autophagy were measured to explore the model of cell death during DFO radiosensitization. Intracellular calcium levels, cell cycle, and ROS levels were examined to study the mechanism of the cell death. ***Results: We found that DFO enhanced X-ray-induced growth inhibition of U251 cells. Increased protective autophagy, occurring in U251 cells the first day of being treated with DFO and X-rays, rendered the radiosensitivity enhancement of DFO insignificant. However, the radiosensitizing effect was clear from the fourth day, which was attributed to the increase of apoptosis and decrease of protective autophagy. Further investigation revealed that the high level of apoptosis induced by DFO plus X-rays was dependent on the level of cytoplasmic calcium because the apoptosis was inhibited by [1,2-bis(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid], a cytoplasmic calcium chelator. ***Conclusion:*** Our results clearly demonstrate that DFO can enhance the radiosensitivity of U251 cells by increased calcium-dependent apoptosis.

Keywords: *Radiosensitivity, Deferoxamine, Apoptosis, Autophagy, Intracellular calcium.*

INTRODUCTION

Radiotherapy is one of the main therapeutic methods for cancer treatment. Despite recent advances in radiation oncology, biological response and sensitivity of cancer cells to radiotherapy vary considerably among patients [(1)]. These differences are most likely induced by variations in resistance of cancer cells to radiation. Radiosensitizers are usually pharmacological or chemical agents that act synergistically with radiation to significantly decrease the resistance of cancer cells via an increase of cell death. Consequently, the identification of effective radiosensitizers to enhance the radiosensitivity of cancer cells is a

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major challenge faced in the field of radiotherapy.

Iron, one of the most significant elements in the body, is required in various biological processes such as oxygen delivery, electron transfer, energy metabolism, DNA synthesis, and cell cycle regulation [2]. Therefore, iron is frequently regarded as a key element for sustaining life. Nevertheless, iron is also closely associated with the biological behavior of cancer cells. High dietary intake of iron is reported to correlate with increased tumor oncogenesis [3] and development [4]. In addition, cancer cells often exhibit several alterations in the cellular metabolism of iron, especially in the processes of uptake, storage, and transport. For example, a high level of transferrin receptor and ferritin, as well as a low level of ferroportin-1 expression, are found in breast [5], lung [6], and prostate cancer cells [7]. As an increase in transferrin receptor and ferritin levels leads to increased uptake and storage of iron, and a decrease in ferroportin-1 level results in decreased iron efflux from cells, the iron metabolism in cancer cells is thought to promote intracellular iron accumulation. Based on the effect of iron on oncogenesis and proliferation of cancer cells, we propose that iron can be regarded as an important target for cancer therapy

Deferoxamine (DFO), which chelates the ferric ion from proteins, has a long history of clinical use to treat transfusional iron overload as a method to excrete the excess iron. Some studies have suggested that DFO has effective anti-tumor activity both *in vivo* [8] and *in vitro* [9]. Iron depletion, which promotes G1/S arrest and apoptosis [10], is believed to be the mechanism of DFO-induced cytotoxicity. As X-rays also induce apoptosis and cell cycle arrest in cancer cells, we hypothesized that DFO can function as a radiosensitizer. To date, minimal research has been focused on interfering with iron metabolism as a radiosensitizing strategy.

The radiosensitizer acts synergistically with radiation to increase the lethal effect on cancer cells. Although the cell death induced by radiation combined with sensitizers may be different from that induced by radiation alone, the former is commonly categorized as ionizing radiation-induced cell death. The ionizing radiation-induced cell death includes necrosis, apoptosis, and autophagy [11]. Recent studies have demonstrated that apoptosis and autophagy can interconvert into each other, which makes the mechanisms associated with radiation-induced cell death more complicated [12]. In this paper, we explored the function of DFO as a radiosensitizer and the corresponding mechanisms required for DFO to enhance the radiosensitivity. First, the radiosensitivity enhancement of DFO on human glioma U251 cells was studied. Then, the models of cell death induced by DFO plus X-rays were examined. Finally, the mechanism for the cell death was explored.

MATERIALS AND METHODS

Cells and reagents

Human glioma U251 cells were obtained from the School of Biological Science and Medical Engineering of Southeast University (Nanjing, China). DFO, 2',7'-dichlorodihydrofluorescein diacetate (DCF-DA), 3-methyladenine (3-MA), fluo-4 AM, and [1,2-bis(2-aminophenoxy)ethane -N,N,N',N'-tetraacetic acid] (BAPTA-AM) were purchased from Sigma Chemical (St. Louis, MO, USA). A CCK-8 Counting Kit, Apoptosis Detection Kit, Caspase-3 Activity Kit, and Propidium Iodide (PI)/RNase Staining Kit were obtained from Beyotime Institute of Biotechnology (Shanghai, China). Cyto-ID Autophagy Detection Kit was purchased from Enzo Life Sciences (Plymouth Meeting, PA, USA). All cell culture reagents were purchased from Thermo Fisher Scientific (Shanghai, China).

Cell culture and irradiation treatment

U251 cells were grown in Dulbecco's modified Eagle's medium containing 10% fetal bovine serum, and 100 U/ml of penicillin and streptomycin. The cells were maintained at 37 ° C in a humidified incubator with 5% CO_2 and 95% air. The cells were treated with DFO for 1 h, and then they were irradiated with 6-MeV X-rays (200 cGy/min) from a linear accelerator (Varian Medical Systems, Palo Alto, CA, USA).

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After 1 day of incubation, the culture media containing DFO was removed.

Cell viability assay

The cytotoxicity of DFO on U251 cells was studied with a cell viability assay. U251 cells were treated with different concentrations of DFO (0, 50, 100, 500, 1000, and 10000 μM). The cell viability was estimated using the CCK-8 Counting kit according to the manufacturer's instructions.

As for the viability of U251 cells on the first day after DFO radiosensitivity, the cells were treated with DFO (50 or 100 μM) 1 h before exposure to 6 Gy of X-ray. To study the function of autophagy, the cells were treated with 3-MA 1 h before exposure to 6 Gy of X-ray. The remainder of the procedures was the same as those performed for the cytotoxicity assay of DFO.

Clonogenic formation assay

The cells were treated with DFO (50 and 100 μM) for 1 h before being exposed to X-rays at doses of 0, 2, 4, 6, or 8 Gy. Following another 9 days of incubation, the colony forming ability of the cells was estimated using a clonogenic formation assay [13].

Apoptosis determination

The cells were treated with DFO or /and BAPTA-AM (10 μM; dissolved in DMSO) for 1 h and then exposed to 6 Gy of X-ray. After different durations of incubation, the cells were stained with Annexin V/ PI and analyzed with a flow cytometer (BD Biosciences, Franklin Lakes, NJ, USA) according to the manufacturer's instructions.

Autophagy analysis

The cells were treated with DFO for 1 h and exposed to 6 Gy of X-ray. One or four days later, cells were stained with Cyto-ID green autophagy detection reagent and analyzed with the flow cytometer according to the manufacturer's instructions.

Caspase-3 activity assay

Caspase-3 activity was determined based on the ability of caspase-3 to change acetyl-Asp-Glu -Val-Asp p-nitroaniline into p-nitroaniline. U251 cells were treated with DFO 1 h prior to 6 Gy of X -ray exposure and cultured for 8 days. The change in caspase-3 activity was then quantified with a Caspase-3 Activity Kit [14].

Measurement of intracellular calcium level

U251 cells were treated with DFO 1 h before exposure to 6 Gy of X-ray. Four days later, the cells were incubated with fluo-4 AM (5 μM), and the level of intracellular calcium was measured using flow cytometry according to the manufacturer's protocol.

Cell cycle analysis

The cells were treated with DFO for 1 h and followed by 6 Gy of X-ray. Four days later, the cell cycle analysis was implemented using PI/ RNase staining [13].

ROS determination

U251 cells were pretreated with DFO and 6 Gy of X-ray, followed by 4 day of incubation. The change in cytoplasmic ROS level was then detected with the DCF-DA method described previously [14].

Statistical analysis

Data are presented as mean ± standard deviation of three independent experiments and were processed with OriginPro 8.0 (Origin Lab, Northampton, MA, USA). One-way analysis of variance and a Duncan test were used to analyze the difference between the untreated and treated groups. A p-value of less than 0.05 was considered to indicate statistically significant differences between groups.

RESULTS

Radiosensitization of U251 cells by DFO

Before exploring the effect of DFO on the radiosensitivity enhancement, the cytotoxicity of DFO on U251 cells for 24 h was detected using the CCK-8 Counting assay. Treatment with DFO caused a concentration-dependent reduction in

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the viability of U251 cells (figure 1a). The value of the half maximal inhibitory concentration obtained for DFO was 827.30 μM. DFO concentrations for induction of mild cytotoxicity (≤20%) were 50 and 100 μM, which were selected for the subsequent experiments of radiosensitivity enhancement.

The radiosensitizing data for DFO are shown in figure 1b. Reduction in the surviving fraction of U251 cells treated with DFO (50 or 100 μM) plus 6 Gy of X-ray was much greater than the surviving fraction of cells treated with X-rays alone, and these reductions became more significant as the dose increased. The results indicate that DFO enhances the radiosensitivity of U251 cells.

Increase of protective autophagy within the first day after radiosensitization byDFO

The clonogenic survival fraction of DFO plus X-rays groups reflected the day-9 viability of the treated U251cells. The cell viabilities at different intervals after DFO plus X-rays, as well as their altered mechanisms, should be explored to fully understand the radiosensitization performed by DFO. The cell viability on the first day after treating U251 cells with DFO plus X-rays was then observed. Figure 2a shows the viability of U251 cells as detected by the CCK8 method. The viability of U251 cells did not decrease significantly on the first day after U251 cells were treated with DFO plus X-rays.

To further study the mechanisms associated with the day-1 viability of U251 cells, apoptosis and autophagy were measured. The apoptosis rate of U251 cells treated with DFO plus X-rays exhibited a slight increase compared to that of cells treated X-rays alone (figure 2b); however, this increase had no statistical significance. Cells exhibited a significant increase in autophagy in the DFO plus X-rays groups compared with that in the X-rays group (figure 2c).

Many studies show that autophagy appears to have dual and conflicting functions in oncogenesis. One is facilitating cell survival, and the other is delay of tumor cells formation. Therefore, the function of this increased autophagy needs to be further explored. Three-MA, an autophagy inhibitor, was used to investigate the function of the autophagy induced by DFO plus X-rays. Figure 2d shows that the viability of U251cells significantly decreased in groups receiving a combination of 3 -MA, DFO, and X-rays compared with viability in groups receiving DFO plus X-rays. This indicates that the increased autophagy induced by DFO plus X-rays is protective. Together, these data indicate that apoptosis and autophagy coexist in U251 cells the first day after being treated with DFO and X-rays. The increased protective autophagy balances the apoptosis and results in no significant changes in the viability of U251 cells.

Increase of apoptosis since the fourth day of DFO radiosensitization

We studied apoptosis and autophage of U251 cells the fourth day after U251 cells were treated with DFO plus X-rays. On the fourth day, autophagy in the groups of DFO plus X-rays recovered to the level of that of cells treated with X-rays alone (figure 3a); however, the apoptosis rate increased significantly (figure 3b). These data suggest that the increased apoptosis and the decreased protective autophagy mutually contribute to the fourth day's effect of DFO on radiosensitivity enhancement.

We then observed apoptosis of U251 cells on the eighth day after U251 cells were treated with DFO plus X-rays. The increased apoptosis rate still existed (figure 3c), which was further supported by elevation of caspase-3 activity in DFO plus X-rays groups (figure 3d). Moreover, the increased rate of apoptosis on the eighth day was more significant than that on the fourth day (figure 3b and 3c). Thus, the eighth day's effect of DFO on radiosensitivity enhancement was primarily due to the higher apoptosis rate of U251 cells.

Increase of intracellular calcium inducing apoptosis in U251 cells

The cellular mechanisms underlying the increased apoptosis rate induced by treatment with DFO plus X-rays were investigated by testing apoptosis-associated factors including intracellular calcium, cell cycle, and ROS. Figure

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4a shows the level of cytoplasmic calcium ions in U251 cells 4 days after being treated with DFO plus X-rays. The calcium ions in DFO plus X-rays groups increased in a concentration-dependent manner. We then pretreated U251 cells with BAPTA-AM, a cytoplasmic calcium chelator, and DFO before exposure to X-rays. Treatment with BAPTA-AM reduced the apoptosis rate induced by co-treatment with DFO and X-rays (figure 4b). This result indicates that elevation of cytoplasmic calcium ions contributes to the increased apoptosis rate in U251 cells treated with DFO plus X-rays.

Four days after being treated with 50 μM of DFO plus X-rays, U251 cells were arrested in S phase; however, when the concentration of DFO increased to 100 μM, U251 cells were arrested in G1 phase. Similarly, DFO at either 50 μM or 100 μM also induced S or G1 phase arrest to the same extent (figure 4c). Thus, the cycle arrest of U251 cells was due to DFO, not DFO plus X-rays. In addition, the effect of DFO on the survival fraction of U251 cells was different from that of DFO plus X-rays, which did not significantly decrease the survival fraction of U251 cells (figure 1b). Therefore, the S or G1 phase arrest induced by DFO did not significantly increase the death of U251 cells. Correspondingly, these data suggest that the S or G1 phase arrest induced by DFO plus X-rays cannot induce the death of U251 cells. Furthermore, these results also indicate that changes in the cell cycle do not contribute to the increased apoptosis rate because the death of U251 cells in the process of DFO's radiosensitivity enhancement is primarily attributed to the elevated apoptosis rate. Figure 4d shows the ROS level of U251 cells 4 days after being treated with DFO plus X-rays. Compared with the X-rays group, the ROS level in DFO plus X-rays groups presented no obvious change. This result suggests that ROS does not contribute to the increased apoptosis of U251 cells. Together, these data indicate that the increased apoptosis rate in U251 cells treated with DFO plus X-rays is attributed to the elevation of cytoplasmic calcium ions.

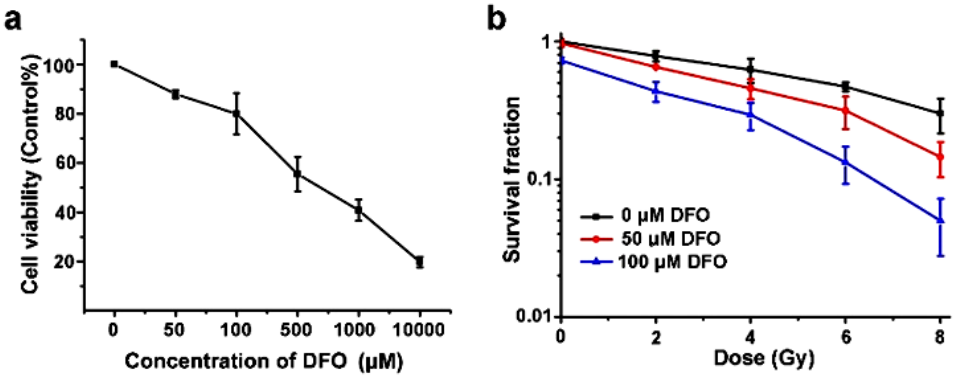


Figure 1. Radiosensitization of U251 cells by DFO. **(a)** The viability of U251 cells 24 h after being treated with DFO at various concentrations (0, 50, 100, 500, 1000, and 10000 μM). **(b)** Survival fraction of U251 cells 9 days after being treated with DFO (0, 50, and 100 μM) plus X-rays (0, 2, 4, 6, and 8Gy).

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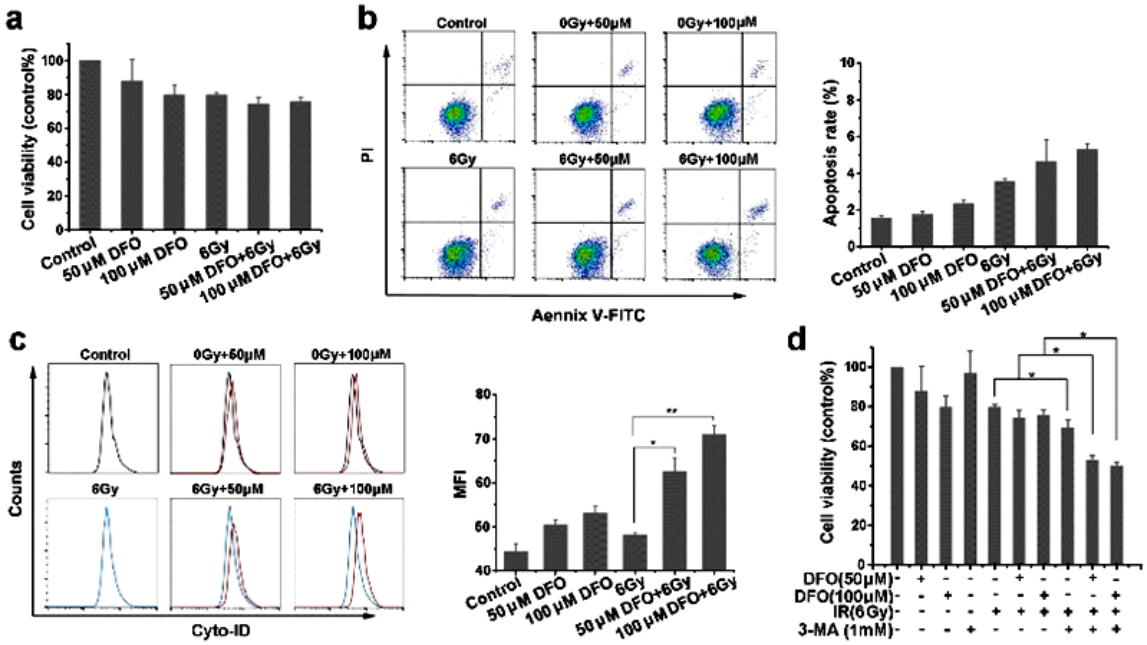


Figure 2. The viability of U251 cells and its corresponding mechanisms 1 day after being treated with DFO and 6 Gy of X-ray. **(a)** Viability rate of U251 cells. **(b)** Apoptosis rate of U251 cells. **(c)** Autophagy of U251cells. **(d)** Viability of U251 cells 1 day after being treated with 3-MA, DFO, and 6 Gy of X-ray. MEI: mean fluorescent intensity. *p<0.05 and **p<0.01

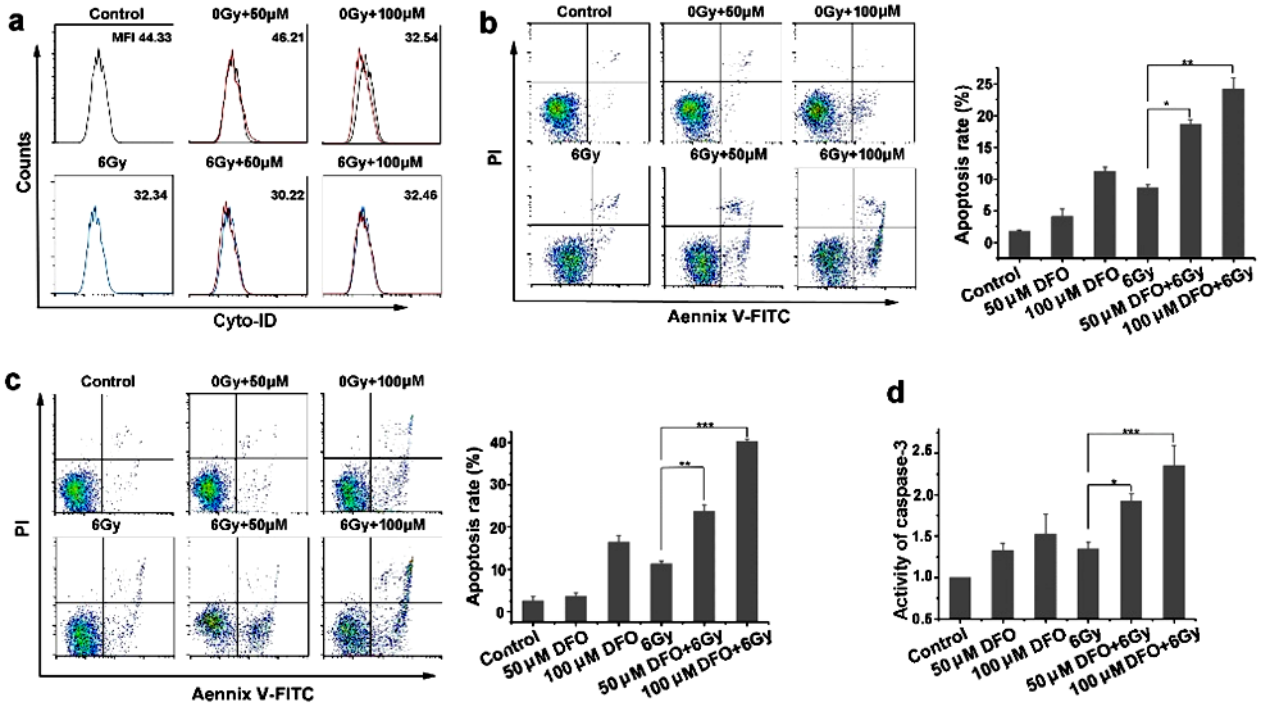


Figure 3. Increased apoptosis rate contributing to the cell death since the fourth day of DFO's radiosensitization. **(a)** Autophagy of U251 cells 4 days after being treated with DFO and 6 Gy of X-ray. **(b)** Apoptosis rate of U251 cells 4 days after being treated with DFO and 6 Gy of X-ray. **(c)** Apoptosis rate of U251 cells 8 days after being treated with DFO and 6 Gy of X-ray. **(d)** Caspase-3 activity of U251 cells the eighth day of being treated with DFO plus 6 Gy of X-ray. *p<0.05, ** p<0.01, and ***p<0.001.

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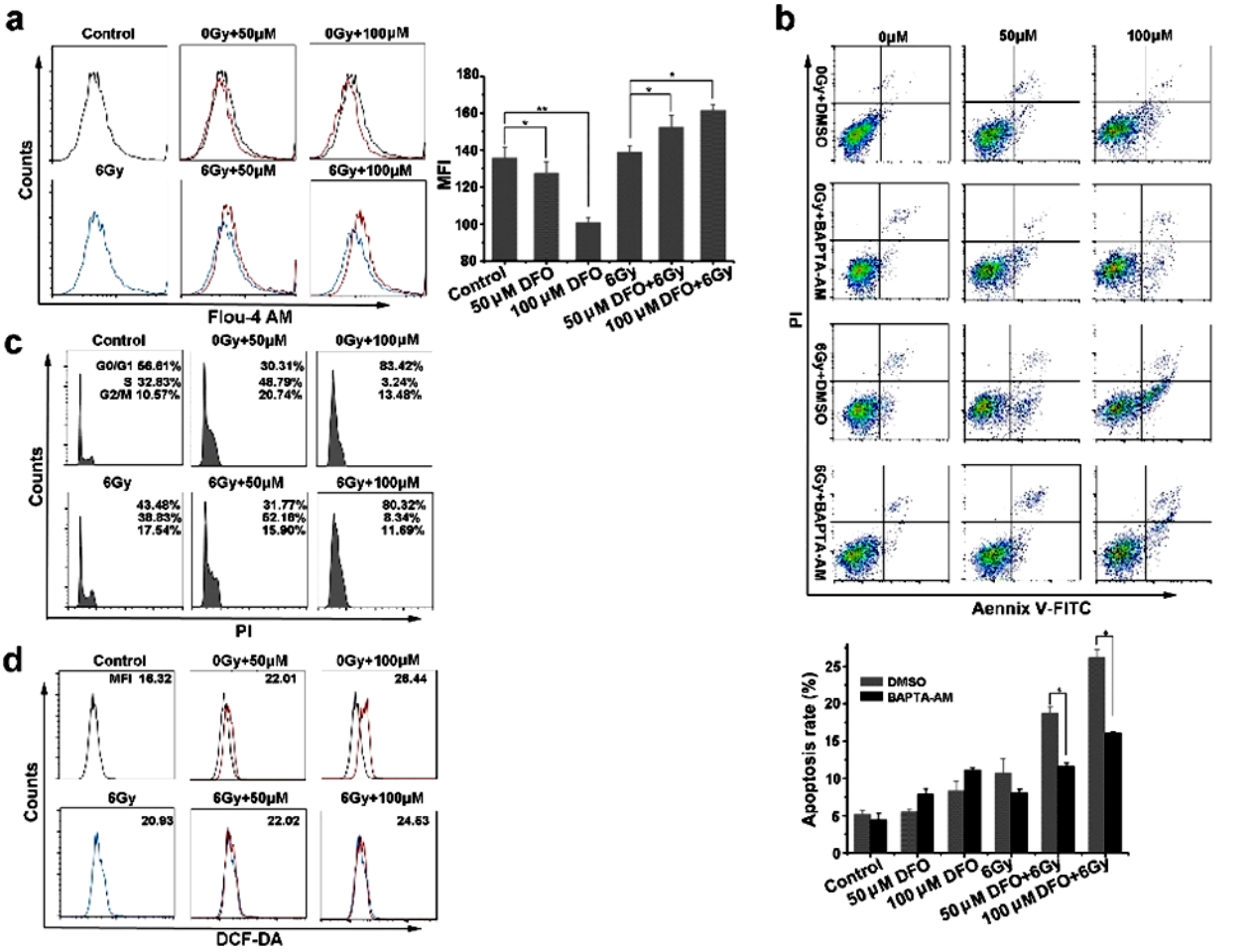


Figure 4. Increased cytoplasmic calcium ion concentration inducing apoptosis of U251 cells the fourth day of being treated with DFO and 6 Gy of X-ray. **(a)** Level of calcium ion concentration in U251 cells. **(b)** Decreased apoptosis rate in U251 cells induced by BAPTA-AM. **(c)** Cell cycle distribution of U251 cells. **(d)** ROS level in U251 cells. *p<0.05 and **p<0.01.

DISCUSSION

One of the main therapies for gliomas is radiotherapy. As gliomas are known to be particularly radioresistant, much attention has been focused on the effort to increase the radiosensitivity of gliomas. DFO is a traditional iron chelator used for the treatment of iron overload. However, in this study, our results reveal that DFO can also act as a radiosensitizer to increase radiosensitivity of human glioma U251 cells via the increased level of calcium-dependent apoptosis.

Radiosensitivity enhancement-induced cell death is a process that is very complex. In DFO-mediated radiosensitivity enhancement, the rate of cell death on the first day was not very significant (figure 2a) due to the occurrence of cytoprotective autophagy of U251 cells (figure 2c and 2d). Generally, autophagy induced by radiation combined with a radiosensitizer exhibits a cytotoxic function [15]. Nevertheless, the cytoprotective autophagy we observed has also been reported after radiosensitivity enhancement with Ag nanoparticles in U251 cells [16]. The multiple functions of autophagy during radiosensitivity enhancement may be dependent on the tumor type and the treatment conditions. As the time progressed, the cytoprotective autophagy was no longer able to resist the cellular damages induced by DFO plus X-rays, and the autophagy recovered to the level of that upon X-rays treatment alone on the fourth day (figure 3a).

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Concurrently, the rate of apoptosis gradually increased (figure 2b, 3b and 3c) and became the major force of DFO's radiosensitization. DFO-induced iron depletion can decrease proliferation and induce apoptosis [17-19]. In addition, radiation can also induce apoptosis through extrinsic or intrinsic signaling pathways. Therefore, the increased rate of apoptosis in U251 cells during DFO's radiosensitization is due to the synergistic effect of DFO and radiation. Turner *et al.* have also reported that tachpyridine, a new iron chelator, can act as a radiosensitizer for HCT116 cells [20]. The corresponding mechanism is through G2 phase arrest. The results demonstrate that chelating iron can be used as a means to enhance the radiosensitivity of tumor cells. However, we should be cautious when using iron depletion in radiosensitization. This caution derives from reports indicating that DFO is inessential for the efficiency of radiotherapy in rat with gliomas-35 [21], or it can even protect cerebellar granule cells from radiation-induced death via blocking iron-related ROS production [22]. The variable effects of DFO in combination with radiation may be due to the types of cells used, as various cell types are differentially sensitive to distinct iron concentrations that can produce different fates of a cell, i.e. proliferation or death [17, 23].

The cell death in a colony forming assay includes an early interphase death and a later reproductive death. Apoptosis is sometimes regarded as the reproductive death [11]. In this study, the effect of DFO is primarily attributed to the increased rate of apoptosis that occurred at the late stage of DFO's radiosensitization. Therefore, we support the view that apoptosis can be considered as a form of the reproductive death.

Our results indicated that the increase of intracellular calcium ion concentration, not changes in cell cycle or ROS level, contributed to the high apoptosis rate in U251 cells that was induced by DFO plus X-rays. It is well known that the increase of intracellular calcium ion concentration is one of reasons for radiation-induced apoptosis. Nevertheless, there are few reports on the iron chelator plus radiation affecting the homeostasis of calcium ions. Both iron and calcium ions are divalent, and a recent study has established a close relationship between iron and calcium homeostasis [24]. For instance, stress that occurred in the endoplasmic reticulum, an intracellular calcium pool, was linked to the iron homeostasis [25]. Hepcidin, the only regulator of the systemic iron level, increases the intracellular calcium level in human osteoblasts [26]. In addition to the study regarding the relationship between iron and calcium metabolism, Leman and Emre have reported that iron depletion by DFO increases the calcium level in K562 cells [27], which supports the result that DFO plus radiation can induce an increase of intracellular calcium concentration.

In conclusion, we demonstrated that DFO acts as a radiosensitizer in U251 cells, and the calcium-dependent apoptosis primarily contributes to the effect of DFO on radiosensitivity. Further investigation of DFO's radiosensitization should be performed in an animal glioma model to explore the efficacy of this promising radiotherapy.

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***Conflicts of interest*: Declared none.**

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