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Boron neutron capture therapy dramatically promotes secretion of high mobility group box-1 and expression of programmed death-ligand 1.

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Background

Boron neutron capture therapy (BNCT) is a cancer treatment that uses thermal neutrons to produce boron-10 (10B) ions, which then release alpha particles and high mobility group box-1 (HMGB1), which promote angiogenesis. HMGB1 is a secreted protein that is released from dying cells and is a key factor in the pathogenesis of cancer. In this study, we investigated the effect of BNCT on the secretion of HMGB1 and the expression of programmed death-ligand 1 (PD-L1) in tumor cells.

AIM

In this study, we investigated the effect of the secretion of HMGB1 and the expression of programmed death-ligand 1 (PD-L1) in tumor cells.

Materials/Methods

Human glioblastoma (U87) cells and human glioblastoma (U87) cells were used in this study. The cells were treated with BNCT or 10B ions. The expression of HMGB1 and PD-L1 was measured by Western blotting and ELISA. The secretion of HMGB1 was measured by ELISA. The expression of PD-L1 was measured by Western blotting and ELISA. The expression of HMGB1 and PD-L1 was measured by Western blotting and ELISA. The secretion of HMGB1 was measured by ELISA. The expression of PD-L1 was measured by Western blotting and ELISA.

Results

The results of the Western blotting are shown in Fig. 1. The expression of HMGB1 and PD-L1 was significantly increased in the BNCT group compared to the control group. The secretion of HMGB1 was significantly increased in the BNCT group compared to the control group. The expression of PD-L1 was significantly increased in the BNCT group compared to the control group.

Conclusion

Our results suggest that BNCT promotes the secretion of HMGB1 and the expression of PD-L1 in tumor cells. This suggests that BNCT may be a promising treatment for cancer.



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Evaluating the risk of fatal radiation-induced secondary malignancies for patients receiving boron neutron capture therapy

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Introduction

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Materials and methods

Human glioblastoma (U87) cells and human glioblastoma (U87) cells were used in this study. The cells were treated with BNCT or 10B ions. The expression of HMGB1 and PD-L1 was measured by Western blotting and ELISA. The secretion of HMGB1 was measured by ELISA. The expression of PD-L1 was measured by Western blotting and ELISA.

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The results of the Western blotting are shown in Fig. 1. The expression of HMGB1 and PD-L1 was significantly increased in the BNCT group compared to the control group. The secretion of HMGB1 was significantly increased in the BNCT group compared to the control group. The expression of PD-L1 was significantly increased in the BNCT group compared to the control group.

Conclusion

Our results suggest that BNCT promotes the secretion of HMGB1 and the expression of PD-L1 in tumor cells. This suggests that BNCT may be a promising treatment for cancer.



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Tirapazamine, a hypoxic cytotoxin, inhibits induction of cancer stem cell-like cells by X-irradiation.

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Background/Aim

- The induction of cancer stem cell-like cells (CSCs) by irradiation depends on an important factor in the acquisition of stem cell properties: hypoxia. Hypoxia is a key factor in the induction of CSCs because of its ability to suppress cell death.
- Tirapazamine (TIPAZ) is a hypoxic cytotoxin that selectively kills hypoxic cells. It is known to inhibit the induction of CSCs by irradiation.
- In this study, we investigated the effect of TIPAZ on the induction of CSCs by irradiation in human glioblastoma cells.

Materials/Methods

- Human glioblastoma cells were irradiated with 2 Gy or 4 Gy in the presence or absence of TIPAZ.
- The induction of CSCs was assessed by sphere formation assay and flow cytometry analysis.
- The expression of hypoxia-inducible factor-1 (HIF-1) and stem cell markers was analyzed by Western blotting and qPCR.

Results

- Irradiation significantly increased the number of CSCs in human glioblastoma cells.
- TIPAZ treatment significantly inhibited the induction of CSCs by irradiation.
- TIPAZ treatment also inhibited the expression of HIF-1 and stem cell markers.

Conclusion

TIPAZ treatment inhibits the induction of CSCs by irradiation in human glioblastoma cells, suggesting that TIPAZ may be a potential therapeutic agent for glioblastoma.



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Possibility of HIF-1 target therapy for the hypoxic cells resistant to boron neutron capture therapy

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INTRODUCTION

The biological effect of boron neutron capture therapy (BNCT) depends on the boron dose from ¹⁰B(n,^α)¹¹B reaction, therefore the uptake of ¹⁰B is a key factor. ¹⁰B-sarcosine (BNA) which has been used the most frequently in BNCT is taken in by cancer cells through the L-type amino acid transporter 1 (LAT1) by extracellular transport of other amino acids. Although it is known that the uptake of ¹⁰B-BNA into tumor cells is suppressed under hypoxic condition, the molecular mechanism of hypoxia-induced modulation on suppression in the boron uptake is not clarified. Therefore, in this study, we aimed to evaluate to clarify the relationship between LAT1, hypoxia-inducible factor-1 (HIF-1) and BNA uptake and hypoxia-inducible factor 1 (HIF-1) which is activated by hypoxia.

MATERIALS AND METHODS

Materials

[Cell lines] T86G (human glioblastoma cells) / HSC-2 (human breast adenocarcinoma cells) / T86G cells were grown in Dulbecco's modified Eagle medium/nutrient mixture F-12 and the others were grown in Dulbecco's modified Eagle medium. Both mediums were supplemented with penicillin, streptomycin, and 10% FBS.

Methods

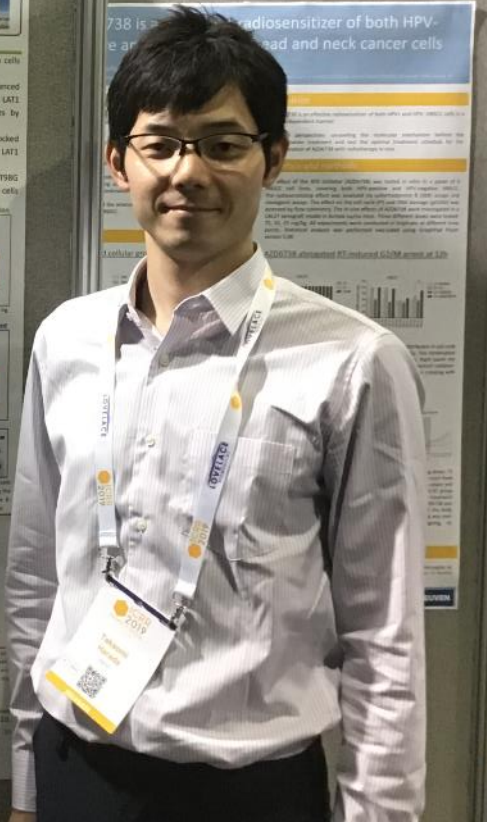
- To elucidate mechanism of the attenuation of the effect of BNCT caused by hypoxia, deferazemicin (DFZ) which is a hypoxic-mimetic agent was used for experiments.
 - Cells were incubated under normoxia (21% O₂), hypoxia (1% O₂), or 5 μM DFZ for 24 h. Then protein expression of HIF-1α was evaluated by western blot analysis and gene expression of LAT1 was assessed by real-time reverse transcription polymerase chain reaction (RT-PCR).
 - After 24 h incubation, cells were treated with ¹⁰B-BNA for 2 h, and after that, the boron accumulation in cells was evaluated by inductively coupled plasma atomic emission spectrometry (ICP-AES).
- To clarify the relationship between HIF-1α and LAT1, gene expressions were evaluated by using the HIF-1α gene knockdown technique. Cells were incubated for 24 h after suppressing HIF-1α expression using siRNA. As for the evaluation of LAT1, cells were incubated for 24 h under 5 μM DFZ after using siRNA. Gene expression was assessed using qRT-PCR.
- In order to improve the effect of BNCT in hypoxic cells, BNCT combined with HIF-1 inhibitor, YC-1 was administered in cell cultures and after 24 h incubation under hypoxia, cells were treated with BNA for 2 h, then exposed to an accelerator-based neutron beam with the irradiation charge amount of 0.6 C/kg a neutron beam current. Following irradiation, chromosome assays were carried out. The outline of experiments were shown in Fig. 1.

RESULTS AND DISCUSSION

- In hypoxic condition, LAT1 mRNA expressions and boron accumulations in cells were suppressed (Fig. 2).
- The simulated hypoxic environment induced by DFZ was confirmed by enhanced protein expression of HIF-1α compared with cells under normoxia (Fig. 4). LAT1 expressions and boron accumulations were suppressed in all cell lines by treatment with 5 μM DFZ (Fig. 3).
- In treated cells with 5 μM DFZ, LAT1 expression was restored in HIF-1α knockdown group in all cell lines (Fig. 5), revealing that HIF-1α acts as suppressing LAT1 expression in hypoxic cells.
- From the results of surviving fraction after BNCT combined with YC-1 in T86G cells, the treatment with YC-1 sensitized the antitumor effect of BNCT in cells cultured in hypoxia (Fig. 6).

CONCLUSIONS

It was shown that hypoxia suppressed LAT1 expression through accumulation of HIF-1 inhibitor, YC-1 has a potential of sensitizing the antitumor effect of BNCT in hypoxic tumor cells.



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