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# Radiobiological effects of cisplatin in carbon-irradiated cancer and bystander normal cells: the involvement of gap junction communication and NRF2 antioxidant system

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**Introduction**
Glioblastoma multiforme (GBM) is the most common and most aggressive human brain tumor. Because most of GBM patients die of their disease and the median overall survival is approximately 1 year. In addition, GBM is difficult to treat since the tumors contain many different types of cell. To this end, the treatment plans for GBM may combine several approaches. Generally, GBM patients are treated with surgical resection together with a combination of radiotherapy and chemotherapy. Even though the plan is implemented, it does not effectively enough to prevent the recurrence and resistance of the tumor during the course follow-up. To date, the mechanisms for recurrence and resistance of GBM to radiochemotherapy that occurs within the irradiated field are not fully examined. To overcome this problem, carbon ions radiotherapy is a promising treatment modality of GBM because it is able to provide a high dose of radiation given to the tumor without the excess damage to normal tissue. Therefore, it would significantly improve survival rates in patients. However, its mechanism of action with chemotherapy in the non-irradiated bystander normal cells surrounding carbon-irradiated cancer cells has not been investigated. To address this question, we perform the in-depth investigation of the effect of combined radiochemotherapy with cisplatin in co-cultured with carbon-irradiated human GBM (T98G) cells and non-irradiated bystander human skin fibroblasts (NB1RGB) with particular emphasis on the role of gap-junction intercellular communication (GJIC) and Nuclear factor (erythroid-derived 2)-like 2 (Nrf2).

**Materials and Methods**
The layered tissue culture strategy that allows isolation of pure non-irradiated bystander normal cells and carbon-irradiated cancer cells was used (Fig. 1). Briefly, confluent T98G cells were treated with cisplatin, followed by carbon ions (Dose 6 Gy, LET 76 keV/um) at the biology experiment port of the Heavy Ion Medical Accelerator in Chiba (HIMAC) at the National Institute of Radiological Sciences (NIRS) in Japan. Within 15-20 min following exposure, carbon-irradiated T98G cells were trypsinzied and seeded on the top of insert with normal human NB1RGB cells in the presence and absence of gap-junction inhibitor (AGA) at the bottom of it. Following co-culture for 5 h, T98G and NB1RGB cells were then harvest and assayed for colony formation, micronucleus formation and western blot.

**Results**
Using this co-culture system our results clearly indicate that GJIC enhances cisplatin toxicity in carbon-irradiated T98G cells and bystander NB1RGB cells. However, the cytotoxicity in the bystander NB1RGB cells can be partially suppressed by inhibiting of GJIC with AGA. The protective mechanism of AGA against the toxic effect of radiochemotherapy was assessed based on the restoration of the antioxidant defenses via activation of Nrf2. With the result obtained, it can be inferred that the activation of Nrf2 might facilitate accumulation of antioxidant enzymes within cells and can affect cell survival by increasing the repair capacity in a community of cells. Therefore, GJIC and Nrf2 significantly influence in the propagation of damaging effects of high-LET carbon ions combined with cisplatin from irradiated cancer cells to non-irradiated bystander normal cells.

**Conclusion**
The finding provides further insight into the radiobiological aspect of high-LET carbon ions for GBM patients

that entails potential implications for clinical radiation oncology. Additional research is needed to focus on new drug with the inclusion of cisplatin that could potentially further improve the overall prognosis of GBM patients.

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