OR1 Significance of Manipulating Tumor Hypoxia and Radiation dose Rate in Terms of Local Tumor Response and Lung Metastatic Potential

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BACKGROUNDS AND PURPOSES: Many cells in solid tumors are quiescent in situ but still clonogenic. Quiescent (Q) tumor cells are thought to be more resistant to low LET radiation because of their larger hypoxic fraction and greater capacity to recover from radiation-induced DNA damage than proliferating (P) tumor cells. Actually, our original method for selectively detecting the response of intratumor Q cells verified those characteristics of Q-cell population and made it possible to evaluate the usefulness of various modalities for cancer therapy in terms of effectiveness against Q-cell populations within local tumors. Based on the characteristics of the response of intratumor Q cells to various DNA-damaging treatments obtained so far, more effective and useful treatment modalities for local tumor control can be developed.

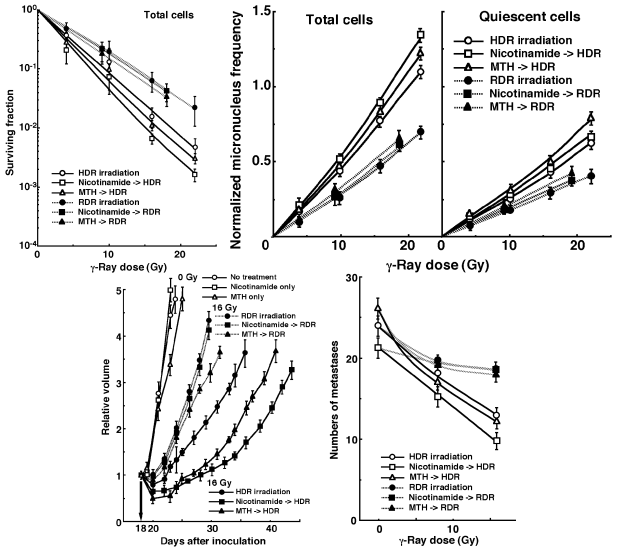
Metastasis is a leading cause of cancer deaths and involves a complex, multistep process by which tumor cells disseminate to distant sites to establish discontinuous secondary colonies. It was reported that acute and cyclic, but not chronic, hypoxia significantly increased the number of spontaneous lung metastases in mice by a factor of about 2, and that this effect was due to the influence of the acute hypoxia treatment on the primary tumor and not to other potential effects of the treatment such as damage to the lung epithelium. Based on this report, we recently reported the significance of injection of an acute hypoxia-releasing agent, nicotinamide, into tumor-bearing mice as a combined treatment with high dose rate (HDR) γ-ray irradiation in terms of repressing lung metastasis. However, when combined with reduced dose rate (RDR) γ -ray irradiation, the significance of manipulating hypoxia within local solid tumors has not yet been clarified in terms of lung metastasis. Meanwhile, concerning local tumor control, it was already reported that manipulating hypoxia in solid tumors during RDR as well as HDR γ-ray irradiation influences the radiosensitivity of local tumors, especially with γ-rays.

Thus, the aim of the current in vivo study is to elucidate the significance of the nicotinamide treatment as a combined treatment with RDR γ-ray irradiation in terms of lung metastases compared with the combination with mild temperature hyperthermia (MTH), which had already been shown to have the potential to manipulate intratumor hypoxia, and preferentially release diffusion-limited chronic hypoxia according to our previous reports. In addition, concerning the local tumor response to γ-ray irradiation with or without nicotinamide or MTH, the effect not only on the total (P + Q) tumor cell population but also on the Q-cell population was also evaluated using an original method of detecting the response of Q cells in solid tumors.

MATERIALS AND METHODS: B16-BL6 melanoma tumor-bearing C57BL/6 mice were continuously given 5-bromo-2'-deoxyuridine (BrdU) to label all P cells. They received γ-ray irradiation at HDR or RDR following treatment with the acute hypoxia-releasing agent nicotinamide or MTH. Immediately after the irradiation, cells from some tumors were isolated and incubated with a cytokinesis blocker. The responses of the Q and total (P+Q) cell populations were assessed based on the frequency of micronuclei using immunofluorescence staining for BrdU. In other tumor-bearing mice, 17 days after irradiation, macroscopic lung metastases were enumerated.

RESULTS: Following HDR irradiation, nicotinamide and MTH enhanced the sensitivity of the total and Q-cell populations, respectively. The decrease in sensitivity at RDR irradiation compared with HDR irradiation was slightly inhibited by MTH, especially in Q cells. Without γ-ray irradiation, nicotinamide treatment tended to reduce the number of lung metastases. With γ-rays, in combination with nicotinamide or MTH, especially the former, HDR irradiation decreased the number of metastases more remarkably than RDR irradiation.

CONCLUSION: Manipulating both tumor hypoxia and irradiation dose rate have the potential to influence lung metastasis. The combination with the acute hypoxia-releasing agent nicotinamide may be more promising in HDR than RDR irradiation in terms of reducing the number of lung metastases [1].



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固形腫瘍内の酸素化状況の操作と照射線量率が局所腫瘍制御と遠隔肺転移能に及ぼす効果　　独自研究

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