Role of HIF-1α in the Response of Tumors to the Combination of Hyperthermia and Radiation *in vivo*

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Background: Mild temperature hyperthermia (MTH) increases blood flow and oxygenation in tumors. On the other hand, high-dose irradiation such as stereotactic body radiotherapy (SBRT) or stereotactic radiation surgery (SRS) damages blood vessels, decreases blood flow and increases hypoxia in tumors, thereby it upregulates hypoxia-inducible factor-1α (HIF-1α) and vascular endothelial growth factor, which promote tumor recurrence and metastasis after radiotherapy. The purpose of the present study was to reveal whether MTH decreases the radiation-induced upregulation of HIF-1α and VEGF, thereby it enhances the efficacy of high-dose radiation against tumors.

Methods: FSaII fibrosarcoma grown subcutaneous in the leg of C3H mice were used. Tumors were irradiated with 15 Gy using ⁶⁰Co irradiator and heated at 41℃ with an Oncothermia heating unit. The blood perfusion and hypoxia were determined with Hoechst 33342 and pimonidazole, respectively. The expression levels of HIF-1α and VEGF in tumor sections were determined with immunohistochemical method. Apoptosis of tumor cells was assessed with terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling (TUNEL) staining and tumor growth was determined.

Results: MTH at 41℃ for 30 min increased blood perfusion and decreased hypoxia whereas 15 Gy irradiation decreased blood perfusion and increased hypoxia in FSaII tumors. The irradiation markedly increased the expression HIF-1α and VEGF in the tumors in 3 days and MTH applied immediately after tumor irradiation significantly prevented the radiation-induced upregulation of HIF-1α and VEGF. MTH significantly increased the effects of radiation to induce apoptosis and suppress tumor growth.

Conclusion: MTH inhibits the radiation-induced upregulation of HIF-1α and VEGF, thereby it enhances the response of tumor to high-dose irradiation. MTH may effectively enhance the efficacy of SBRT or SRS.