

Assessment of rapamycin effects on tumor oxygenation and angiogenesis by using EPRI and MRI

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Abstract

Rapamycin is an inhibitor of mammalian target of rapamycin (mTOR), and inhibits tumor growth and angiogenesis. Rapamycin has radiosensitization effects on some tumors. In radiotherapy and chemotherapy of cancers, partial pressure of oxygen (pO_2) is an important factor to determine treatment outcome. Recently, a novel methodology has been developed that can provide quantitative 3D maps of tissue pO_2 and blood volume images in living animals by using Electron Paramagnetic Resonance Imaging (EPRI) and magnetic resonance imaging (MRI) [1,2]. EPRI with triarylmethyl radical as a tracer gives 3D maps of tissue pO_2 level, and MRI with ultrasmall superparamagnetic iron oxide gives blood volume images. In this study, we investigated effects of rapamycin on tumor oxygenation and angiogenesis of living mice by using EPRI and MRI.

Squamous cell carcinoma (SCC) cells (5×10^5 cells) were implanted s.c. into a right hind leg of female C3H Hen MTV mice. Treatment with rapamycin (10 mg/kg b.w./day) and measurements of pO_2 and blood volume were started after 8 days from implantation of the SCC tumor. EPRI measurements were done with a 300 MHz pulsed EPRI system, and MRI measurements were done with a 7 T scanner controlled with ParaVision 3.0.2 (Bruker Bio-Spin MRI GmbH).

Tumor growth in rapamycin treated mice was suppressed compared with non-treated mice. Blood volume in tumor region significantly decreased even after 2 days from beginning of the rapamycin treatment (Fig. 1A). Tumor oxygenation did not drastically change, but pO_2 level slightly increased after 2 days rapamycin treatments, and the average pO_2 value was significantly higher compared with non-treated mice (Fig. 1B). Furthermore, the ratio of hypoxic area to tumor region decreased after 2 days rapamycin treatments, whereas it increased in non-treated mice. These results suggest that rapamycin can normalize blood volume and suppress depletion of oxygen in the tumor region. This higher level of oxygen may contribute to sensitization of tumors to radiotherapy.

[1] Matsumoto K. et al., *Magn. Reson. Med.* **55** (2006) 1157-1163.

[2] Matsumoto S. et al., *J. Clin. Invest.* **118** (2008) 1965-1973.

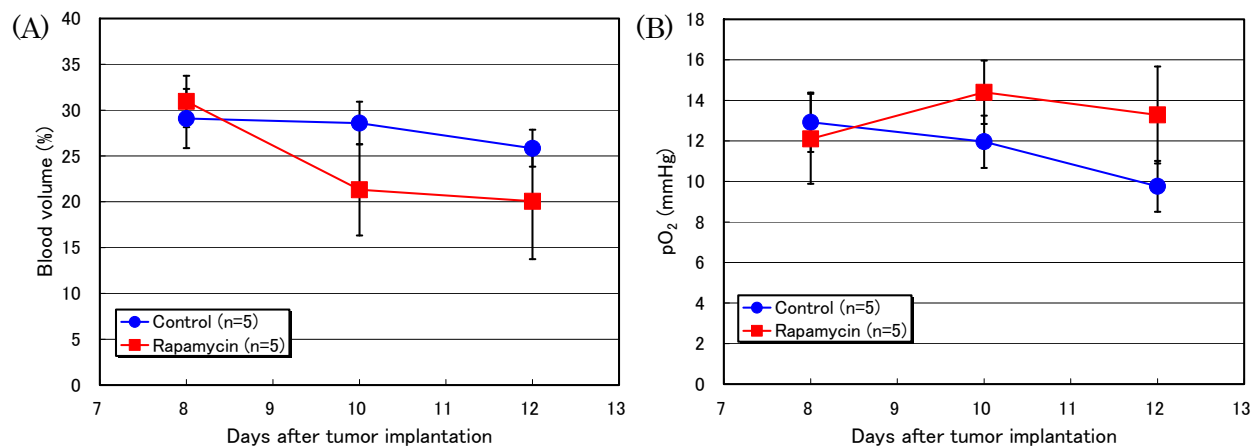


Fig. 1 Changes in median blood volume and pO_2 in tumor region of rapamycin-treated and non-treated control mice.