

Changes in the tumor microenvironment early after irradiation: an EPR oximetry study

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Introduction:

Oxygen partial pressure and blood flow are very important parameters of the tumor microenvironment. There are several studies on variations of this parameters after radiotherapy (1-4), that all show variation in oxygenation status or blood flow 24 h to 48h after irradiation. However, there is a poor knowledge on the changes in the microenvironment at the early stage after irradiation. These informations could be especially relevant for the application in accelerated radiotherapy to give more rationale in the timing between irradiation doses.

Materials and Methods:

Two types of mice tumors were used in this study: FSaII and TLT tumors model injected in gastrocnemius muscle of mice. Oxygen pressure (measured by EPR oximetry with a 1.2 GHz spectrometer, Magnettech, Germany), blood flow (monitored with Laser Doppler Imaging), Interstitial fluid pressure (measured by a wick-in-needle technique) were monitored on tumor when the diameter reach 8 ± 0.5 mm. Irradiation was applied on the tumor using a RX irradiator (Phillips medical, 250 kV, 1.2 Gy/min) with 2, 9, 25 Gy doses. A regrowth delay assay was done with using a single dose of 18 Gy or two doses of 9 Gy with a delay of 4 hours between irradiation.

Results:

In both tumor models, pO₂ increased rapidly after irradiation independently of the irradiation dose in the range of 2 to 25 Gy with a maximal value at 4 hours after irradiation for the FSaII model. After this point, pO₂ decrease slowly till 72 hours after irradiation. (Figure 1). Muscle irradiation with 2 Gy did not show any variation in pO₂ till 72 hours after irradiation. As we observed a maximal pO₂ 4 hours after irradiation, we measure blood flow and interstitial fluid pressure at this time on FSaII tumor. We observed an increase in blood flow of $31 \pm 6\%$ (Figure 2 * $p < 0.01$) and a decrease of $25 \pm 2\%$ (Figure 3 * $p < 0.01$) in IFP 4 hours after a single 2 Gy irradiation. Finally, a regrowth delay assay showed that an irradiation of 2 times 9 Gy (with 4 hours delay) is more effective than a single irradiation of 18 Gy.

Discussion

We demonstrated that pO₂ increased rapidly after irradiation with a maximal value at 4 hours after irradiation (in a range of 2 to 25 Gy) in two tumor models. This maximal value is correlated with an increase in blood flow and a decrease in interstitial fluid pressure. Consumption and permeability measurement, are in progress to further characterize this phenomenon.

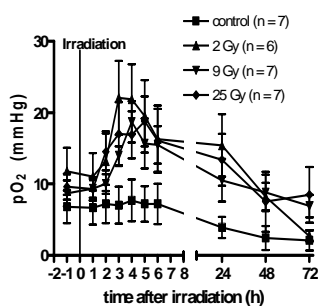


Figure 1: pO₂ (mmHg) (Mean \pm SEM) measured by EPR oximetry before and after irradiation

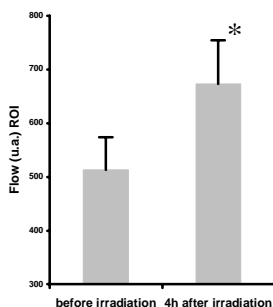


Figure 2: Blood flow measurements using LDI before and 4 hours after irradiation

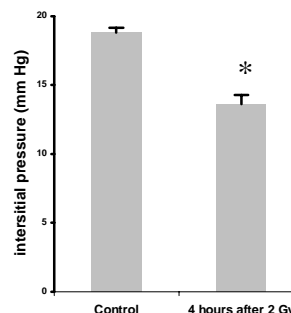


Figure 3: Interstitial pressure measurements measured by the wick-in-needle technique

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