MR characterization of the tumor microenvironment after arsenic trioxide treatment: evidence for an effect on oxygen consumption that radiosensitizes solid tumors

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Introduction
The partial pressure of oxygen (pO₂) is a crucial factor affecting the response of tumors to irradiation and other cytotoxic treatments. It has been predicted that modification of oxygen consumption is much more efficient at alleviating hypoxia than modification of oxygen delivery.

Arsenic has been reported to have anti-tumor effect in acute promyelocytic leukemia and in solid tumors. As₂O₃ seems also to inhibit mitochondrial respiratory function in human leukemia cells. Thus, we hypothesized that As₂O₃ could be an important modulator of tumor oxygenation by affecting the oxygen consumption of tumors. We characterize the evolution of the tumor micro-environment after As₂O₃ treatment.

Materials and methods
The effect of As₂O₃ (5 mg/kg) was studied in a transplantable liver tumor model (TLT) and in a Lewis Lung Caecinoma (LLC). Local pO₂ was measured in vivo using low frequency EPR (1) and ¹⁹F-relaxometry (2). The oxygen consumption rate was measured in vitro using high-frequency EPR. At the maximum pO₂ (after 1h30) perfusion and radiation sensitivity were also studied by Patent Blue staining assay and regrowth delay experiment after X-Ray irradiation (10Gy), respectively.

Results
The administration of As₂O₃ increases significantly the pO₂ (measured by EPR) in TLT and LLC tumors, an effect that was not observed for the control group (Fig.1). The results were confirmed by ¹⁹F NMR relaxometry. The increase in pO₂ induced by As₂O₃ was not due to an increase in tumor perfusion as shown by the Patent blue staining assay (Fig.2). As the increase in pO₂ was not due to an increase in perfusion, the tumor oxygen consumption was investigated. The administration of As₂O₃ significantly decreased the rate of oxygen consumption (Fig.3). Finally, the irradiation (10Gy) of tumors showed a regrowth delay that was significantly increased in arsenic-treated mice.

Conclusion
Arsenic trioxide is an important modulator of pO₂ by decreasing oxygen consumption and enhances the response of tumors to radiotherapy. The time-window for the radiosensitization effect by As₂O₃ can be predicted using MR oximetry techniques (EPR or ¹⁹F NMR relaxometry)