Serial Measurements of Tumour Tissue Oxygen Tension in the Shionogi Model of Prostate Cancer using ^{19}F NMR

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Introduction

Tissue oxygen tension (pO_2) is one of the most important physiological parameters in tumours. It is well known that hypoxic tumours are not only more resistant to radiation therapy, but also more aggressive and less responsive to surgical intervention. Many solid tumours are hormone dependent and hormone withdrawal therapy is frequently used in conjunction with radiotherapy. Studying changes of pO_2 levels in hormone-sensitive tumours with the tumour growth and the hormonal status will provide insight into understanding of the development process of these tumours, and may help in designing more efficient radiation therapy.

We used ^{19}F relaxometry of perfluorocarbons (PFCs) to characterize changes in tumour tissue oxygenation with tumour growth before and after androgen ablation in the Shionogi model of prostate cancer.

Methods

The Toronto subline of the transplantable SC-115 AD mouse mammary carcinoma [1] was used in all experiments. Approximately 5×10^6 cells were injected s.c. into 12 adult male DD/S strain mice. Perfluoro-15-Crown-5-Ether (Exfluor Research Co., Round Rock, TX) was used as the oxygen sensor [2]. Multiple injections of 500 μL of a 40% w/v PFC emulsion (Fresenius-Kabi, Clayton, NC) into a tail vein were carried out at several time points throughout the experiment. When tumour volumes reached 1-2 cm^3, typically 2-3 weeks after the initial injection, androgen ablation was performed through castration by an abdominal incision under isofluorane anaesthesia. Serial pO_2 measurements were performed throughout the growth and regression of the tumours with each mouse being examined app. every three days.

All MR data was obtained using a Bruker/SMIS 2.35T, 40cm horizontal bore imaging spectrometer operating at 94.1 MHz for ^{19}F. An RF surface coil, 2cm in diameter, was used for both spin excitation and signal reception. A pulse-burst saturation recovery pulse sequence with 41 different recovery delays was used to measure T_1 values *in vivo*.

Results

No strong relationship between the tumour size and pO_2 was found, possibly because the majority of the tumours were rather small (<1.6cc). Figure 1 shows pO_2 values measured over time in mice from which both growth and regression data was available (n=6). Oxygenation measurements are plotted on a normalized timeline in which the day of castration is defined as day zero for each mouse. Despite rather large variability between animals, there is a definite trend such that pO_2 values increase up to ca. 7 days following castration.

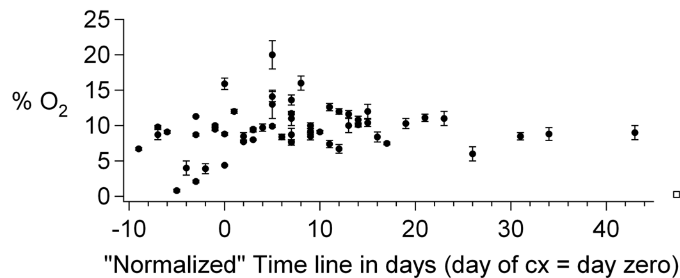

Figure 1. *In vivo* pO_2 measurements using ^{19}F relaxometry of PFC at different time points of the tumour growth cycle.

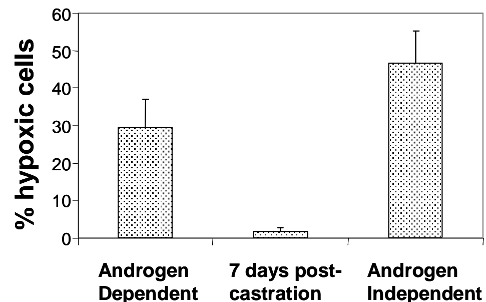

Figure 2. pO_2 measurements using EF5 in Shionogi tumours at 3 different time points of the tumour growth cycle [3].

This result agrees remarkably well with the results of a separate study [3], where the percentage of hypoxic cells was measured in Shionogi tumours throughout tumour growth, using nitroimidazole, EF5 [4] – a hypoxia marker. In particular, the percentage of hypoxic cells reached its lowest point at 7 days post-castration, which correlates well with the onset of a plateau in pO_2 found in our study.

Conclusions

We have demonstrated that serial changes in pO_2 over a long period of time can be measured *in vivo* in the same animals using ^{19}F NMR. The observed changes in tumour tissue oxygenation throughout the tumour growth cycle has important implications in the diagnosis, monitoring and therapy of hormone sensitive tumours.

References

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