Title

Intracellular Water Lifetime as a Tumour Biomarker for diagnosis and therapy outcome by FFC-Relaxometry in breast cancer

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Purpose/Introduction

The diagnostic power of Magnetic Resonance Imaging in tumour phenotyping could be improved observing the marked decrease of T_1 in biological tissues at low magnetic field strength. It is well known that the T_1 of a given tissue changes as a function of the applied magnetic field strength. In particular, the lower is the magnetic field the higher is the differences among tissues. Known as "T_1-dispersion", this phenomenon is a marker of disease and it is invisible to conventional, fixed-field MRI scanners. The Fast Field-Cycling (FFC)-NMR is the only practicable way of measuring it. An overall increase of water content together with an impairment in water exchange across membranes have fundamental role in this behaviour. The measurement of the intracellular water lifetime (τ_{in}) *in vitro* and *in vivo* may bring relevant information on the ongoing metabolism of the tumour cell, as report on the pathological status, grade and therapeutic outcome.

Subjects and Methods

The measurement of τ_{in} was performed *in vitro* and *in vivo* on murine adenocarcinoma cell line (4T1). Different doses of doxorubicin have been tested before the T_1 measurement. The data were analysed using two-site exchange (2SX) model (Fig.1) in which the Bloch equations are modified to describe two-compartments (intra and extracellular) in which water exchange modulates the observed relaxation behaviour.

Results

The most striking result from the fitting procedure is the observation of a significant τ_{in} increase after the first treatment (Fig. 2, 3) due to the slower tumour metabolism caused by doxorubicin, that it was not observed on the corresponding doxorubicin resistant cell line.

Discussion/Conclusion

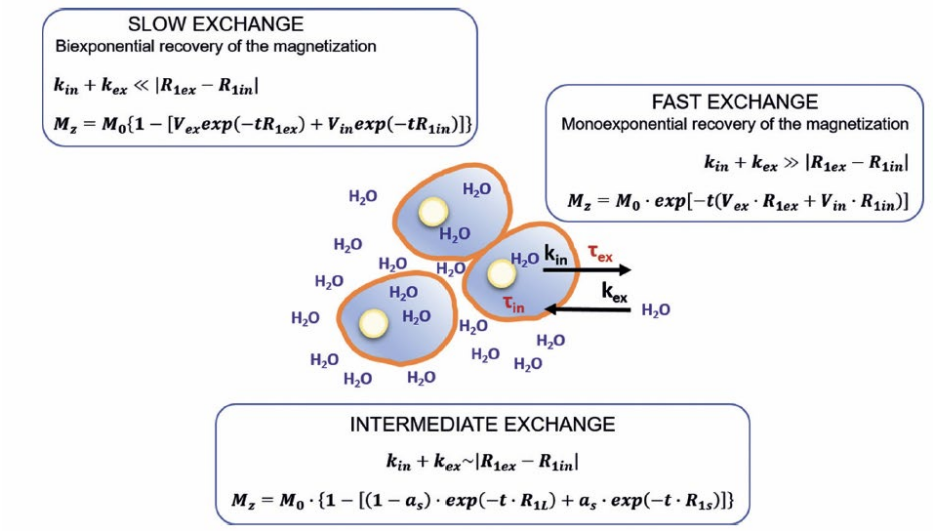
Recently, [1,2] we showed that the τ_{in} represents a hallmark of tumour tissue cells status that can be easily monitored by measuring T_1 at different and relatively low magnetic field strengths. A fast exchange through cell membranes indicates a high metabolic rate and thus a high activity of the tumour cells. Thus it is possible to measure the high metabolic pressure by an enhance water exchange with the exterior of the cell. Therefore, τ_{in} can be considered an important tumour biomarker directly depending on the rate of cell proliferation, cell migration and in responding to external stimuli as hypoxia or extracellular acidosis. Currently, tumour responses to therapy are monitored primarily by imaging evaluating essentially the decrease of tumour size. This approach, however, lacks sensitivity and can only give a delayed indication of a positive response

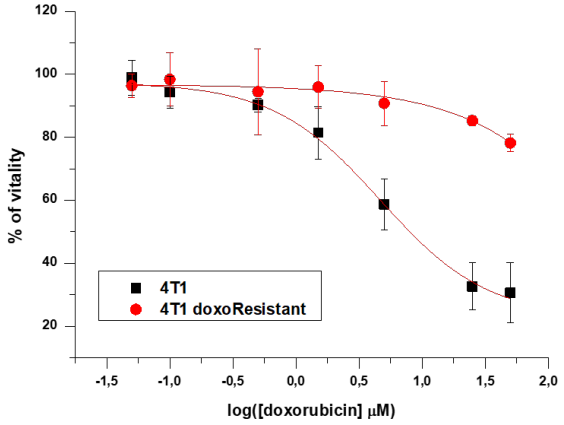
to treatment. In this study, we propose the use of FFC-NMR to provide relevant information about response to treatment by monitoring changes of water exchange rates through cell membranes that are directly dependent on the metabolism alterations caused by the chemo- or radio-therapy.

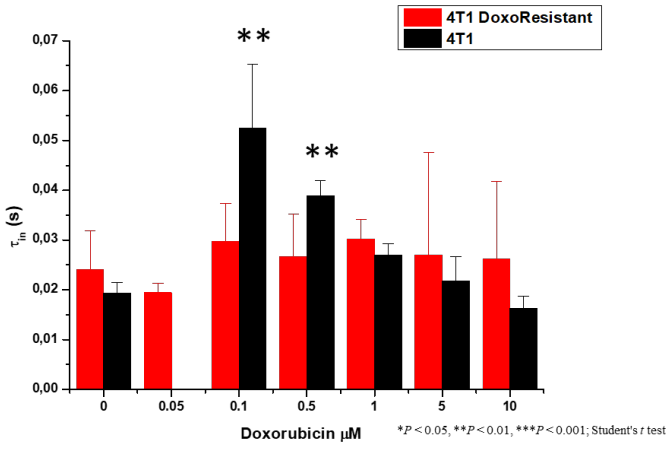
References

[1] MR Ruggiero, et al *Angew Chem Int Ed Engl*, **2018**

[2] MR Ruggiero, et al *Molecular physics* **2018**




% of vitality
log([doxorubicin] µM)
4T1
4T1 doxoResistant


4T1 DoxoResistant
4T1
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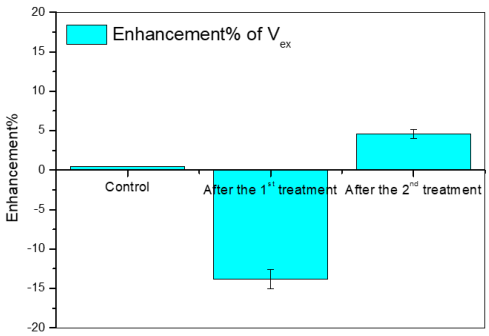
τin (s)
Doxorubicin µM
*P < 0.05, **P < 0.01, ***P < 0.001; Student's t test


Enhancement% of τin
Enhancement%
Control
After the 1st treatment
After the 2nd treatment


Enhancement% of Vex
Enhancement%
Control
After the 1st treatment
After the 2nd treatment