In vivo Fast Field Cycling Relaxometry reports on the extra- and intracellular localization of iron oxide particles in tumou models.(#62)

Maria Rosaria Ruggiero[1], Simona Baroni[1], Valeria Bitonto[1], Smeralda Rapisarda[1], Silvio Aime[1], Simonetta Geninatti Crich[1]

[1] Università degli studi di Torino, torino, Italy

Introduction

The relationship“immune system/tumour”is considered an important hallmark of cancer[1]. Tumour associated macrophages (TAMs) adopt an anti-inflammatory phen secrete factors to promote angiogenesis and tumor invasion.The use of Ultra Small Iron Oxides nanoparticles (USPIO) has been already proposed to the TAM detec generating contrast in $T_{2\text{-weighted}}$ images indipendently of extra and intracellular localization of the NPs. While, T_1 at different fields appear dependent on localization, especially at low field, of the NPs allowing an unambiguous TAM quantification.

Methods

In vitro studies have been carried out on a murine monocyte-derived macrophage cell line (J774) to evaluate the relaxivity changes due to the intracellular localizatic ferumoxytol, clinical negative contrast agent. T_1 were acquired on a FFC relaxometer able to switch over a large range of field stranghts (0.01-20MHz). In order to h mouse, the commercially available relaxometer (Stelar, Mede, Italy) has been modified with the implementation of a 40 mm 0.5T Field Cycling magnet and a dedica solenoid detection coil placed around the anatomical region of interest[2]. The tumour xenografts were prepared by injecting three tumour cell lines (B16 melanoma, 4 168FARN breast carcinoma) in the hindlimb muscle.

Results/Discussion

The relaxivity peak at ca. 8-10 MHz observed in water on ferumoxytol is shifted to lower magnetic field strengths (at 0.5-1 MHz) when the NPs were entrapped in macrophages (Fig.1). For in vivo model, the selected types of tumours (168FARN, 4T1 and B16) are characterized by different amount of necrotic zones and macro infiltrating the tumor stroma. Ferumoxytol was injected at a dose of 0.5 mmol/kg of Fe. The profile obtained 3h and 24h after the injection were significantly different. The profile observed at 24h displays a bell-shaped profile with a maximum around 0.4-0.5 MHz similar to one found for ferumoxytol labelled macrophages. This find clearly indicated the intracellular localization of ferumoxytol as confirmed by histological analysis by the Pearls assay.

Conclusions

The measured T_1 at different field immediately reports on the intra- or extra-cellular localization of the investigated contrast agent. This information could be open ne horizons for cell tracking applications. Despite the herein used prototype FFC-NMR, FFC has recently been applied to MRI, largely thanks to the work of the Lurie gi Aberdeen University where two prototype human whole-body sized FFC-MRI scanners have been built[3].

References

[1] Morita Y, Zhang R, Leslie M, Adhikari S, Hasan N, Chervoneva I, Rui H, Tanaka T. Oncol Lett. 2017;14:2111-2118.

[2] Ruggiero MR, Baroni S, Pezzana S, Ferrante G, Geninatti Crich S, Aime S. Angew Chem Int Ed Engl. 2018, 57:7468-7472.

[3] Pine KJ, Davies GR, Lurie DJ. Magn Reson Med., 2010, 63, 1698-702.

Acknowledgement

This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 668119

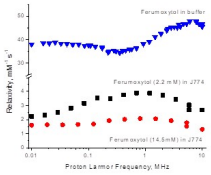

Figure 1

NMRD profiles of J774 cells incubated for 24 h with different ferumoxytol concentrations or with ferumoxytol added to the external buffer. The indicated concentrations refer to the [Fe] in the measured pellets

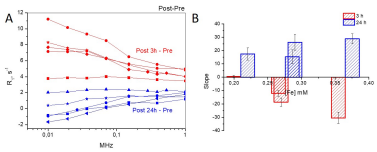

Figure 2

A) NMRD profiles of B16 tumour bearing mouse leg 3 and 24h after (POST) the i.v. injection of ferumoxytol subtracted by the corresponding PRE profile (acquired before ferumoxytol injection). B) Diff initial slopes of the NMRD profiles

Keywords: Iron oxide NPs, labelled macrophage, FFC-NMR