Exploring sensitivity and resolution for cell tracking with Magnetic Particle Imaging: the effects of cell proliferation and intracellular nanoparticle relaxation

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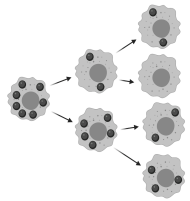
Motivation

Limitation of **Magnetic resonance imaging (MRI)** cell tracking using superparamagnetic iron oxide (SPIO) nanoparticles is the inability to track proliferative cells long-term due SPIO dilution amongst cell progeny [1].



Previous MRI studies have demonstrated that cell division of SPIO agents leads to loss of signal within five to eight generations [2-4]. This is particularly concerning for tracking rapidly dividing cells (cancer).

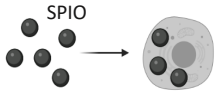
Magnetic particle imaging (MPI) is an emerging modality that overcomes MRI limitations by providing positive contrast and direct quantification

Aim 1: To characterize the dilution of SPIOs in proliferating breast cancer cell line *in vitro* using MPI and histological validation

MPI signal is generated from a combination of Néel (internal rotation of magnetization) and Brownian (physical rotation of nanoparticle) relaxation which is influenced by the nanoparticle's surroundings.

Aim 2: determine how MPI signal and resolution change when SPIOs are intracellular (live cells) compared to free SPIOs (lysed cells).

Methods



Cell Labeling: 4T1 murine breast cancer cells AND Mesenchymal stem cells (MSC) were labeled in vitro by co-incubation with 55 μg Fe/mL ferucarbotran, *with transfection agents (protamine sulfate and heparin)*[5].

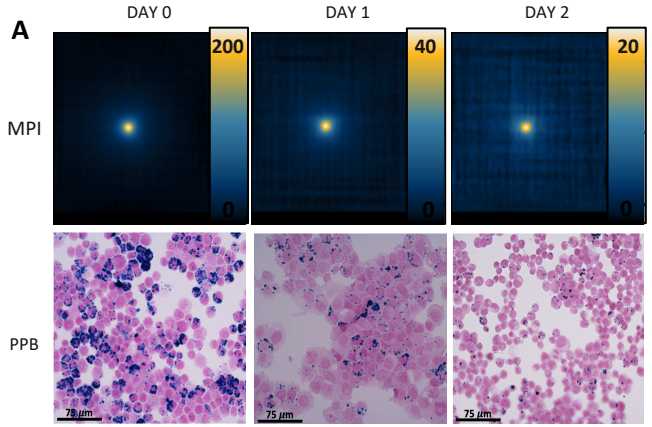
Cell collection: Triplicate samples of 1 x 10^6 ferucarbotran-labeled 4T1 cells were collected after 24 hours (day 0), 45 hours (day 1), and 65 hours (day 2)
Six samples of 2.5x10^5 ferucarbotran-labeled MSC cells were collected. Following imaging MSC were lysed with 70μL RIPA buffer then sonicated.

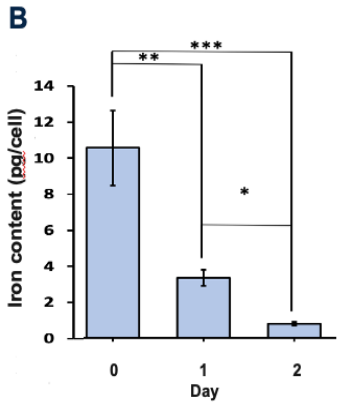
Imaging Protocol: MPI of cells was acquired on a Momentum MPI in 2D using dual-channel 5.7T/m gradients and excitation of 20mT (X-channel) and 26mT (Z-channel). Scan time 1.8 min

MPI Relaxometry conducted for live and lysed cells using rf amplitude 20mT and bandwidth ±160mT

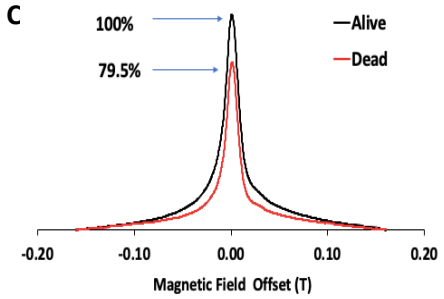
Histological Validation: Each day, a cytospin of 4T1 cells was performed and cells were stained for iron with Perl's Prussian blue (PPB).

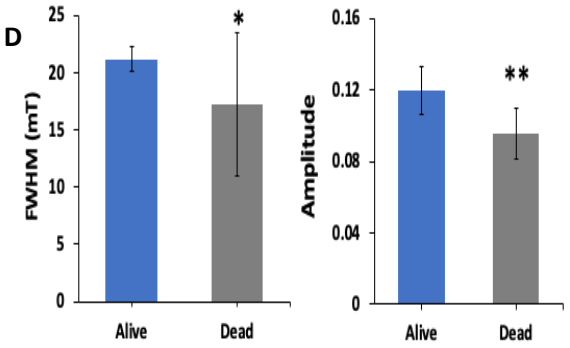
Results





(A) MPI signal for 1 x 10^6 ferucarbotran-labeled 4T1 cells is reduced after collection from culture over 3 consecutive days. PPB stain exhibits sufficient labeling of cells with ferucarbotran labeling (day 0), and reduced iron content as cells proliferate in culture (day 1 and 2). **(B)** Iron mass per cell, measured by MPI, was significantly reduced over time. *p< 0.05 ** (p<0.01) and *** p<0.0001





(C) Average Relaxometry curves for six samples of 2.5 x 10^5 live and lysed ferucarbotran-labeled MSC. **(D)** The peak MPI signal (sensitivity) and Full width half max (FWHM) used to evaluate resolution was significantly lower for ferucarbotran released from lysed cells, compared to live ferucarbotran-labeled cells. *p< 0.00005, **p<0.01

Discussion

Aim 1: The study demonstrated a reduction in MPI signal from SPIO-labeled 4T1 cells following proliferation in vitro. Our measurements of intracellular iron are in close agreement with a theoretical reduction of 66% (day 1) and 87% (day 2).

Aim 2: Lower resolution (higher FWHM) in live ferucarbotran labelled MSC cells likely due to aggregation and increased Brownian relaxation for intracellular SPIOs[5-6] . Decreased sensitivity opposes previous literature MPI sensitivity is expected to be recovered after cell lysis.

Future work will examine this phenomenon in vivo and in other cells types. The reduction in MPI signal for lysed cells is likely related to the release of iron from cells, therefore the experiment must be repeated.

Conclusions

A a decline in MPI signal was generated by SPIO labeled 4T1 cells during proliferation over time, owing to the reduction in intracellular iron content with cell division.

Lysed MSC exhibited a reduction in MPI sensitivity and improved resolution.

MPI cell tracking is in its infancy and these studies contribute important knowledge towards monitoring proliferative cells in vivo and optimizing

References

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