In vivo Serial Monitoring of Implanted Chemically Biotinylated Cells by MRI

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Introduction

The ability to monitor specific cell populations non-invasively is essential for the development and establishment of cell based therapies. Recently, chemical biotinylation of cells have been proposed to enable ready and rapid labelling of all cell types for tracking by MRI [1]. Biotinylated cells can be 'tagged' for MRI using antibodies to biotin conjugated to superparamagnetic iron oxide nanoparticles (SPIOs) or avidin/streptavidin conjugated to SPIOs. In this study, we demonstrate serial MRI of chemically biotinylated SPIO-labelled tumour cells implanted into the flanks of immunocompromised mice over a period of 3 days.

Methods and Materials

Cell labelling

IGROV1 cells (human ovarian epithelial cancer cell line) were chemically biotinylated using an aqueous biotinylation reagent (Fischer Scientific, U.K.). After washing of unreacted biotinylation reagents, half the cell suspension was labeled with anti-biotin SPIOs (Miltenyi Biotec, Bisley, UK) and the other half, mock labeled with anti-H2k SPIOs (Miltenyi Biotec, Bisley, UK): the H2k antigen is not endogenous to IGROV1 cells. Following incubation with SPIOs, both cell populations were separately washed and resuspended in phosphate-buffered saline for implantation in mice.

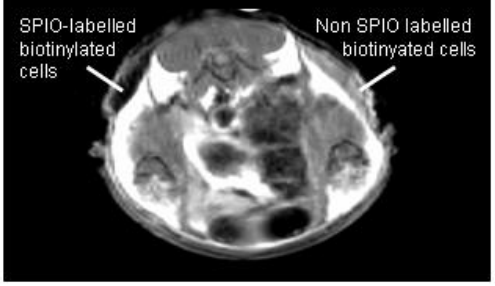
MRI of cells in vivo

SPIO-labeled biotinylated cells (2.5 x 10^7 cells, 170µl) were implanted into one flank of nude balb/c mice (n = 4, Harlan, U.K.) and the equivalent number of non SPIO-labeled biotinylated cells injected into the contralateral flank. MRI was performed just after implantation and at days 1, 2 and 3 after implantation on a 9.4T MR scanner (Varian Inc., Palo Alto, USA); parameters were repetition/echo times = 1300/14ms, field of view = 30x30mm, matrix = 256x128, 2 averages and 5-7 transverse slices of 2mm thickness. Signal intensities (SI) of the cell implants were measured and differences between the implanted SPIO-labelled and non SPIO-labelled cells were tested for significance using the Student's t-test. Following MRI, the implanted cells were carefully dissected along with the covering skin and the underlying mouse muscle and formalin fixed for histological staining with Perls' stain for the presence of SPIOs.

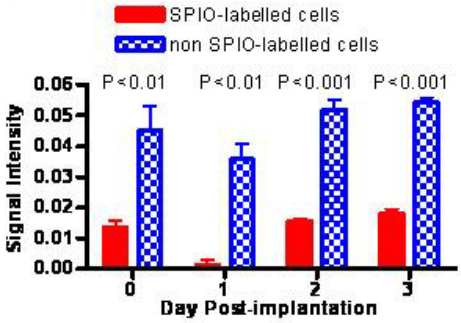
Results and Discussions

Negative enhancement was observed from the implanted SPIO-labelled biotinylated cells compared to the implanted non SPIO-labelled biotinylated cells (Figure). The SI was significantly different immediately after, and at day 1, 2 and 3 day following implantation (Graph). The decrease SI of the SPIO labelled biotinylated cells is consistent with the presence of SPIOs and confirmed by histological Perl's staining (data not shown).

Figure: Transverse MRI image showing negative enhancement of SPIO labelled biotinylated cells compared to non SPIO-labelled cells following implantation in separate flanks of a mouse.



Graph: Signal intensities of both SPIO and non SPIO-labelled cells over a period of 3 days following implantation.



Conclusions

We have shown the feasibility of MRI to monitor SPIO-labelled chemically biotinylated cells over a period of 3 days after implantation. The chemical biotinylation and subsequent tagging of cells with SPIOs may provide a ready and rapid method for the labeling of cells for *in vivo* serial MRI monitoring of cell-based therapies.

References

So, P. W., Kalber, T., Herlihy, A., Bell, J. D., (2006): *Proc. Intl. Soc. Mag. Med.*, 14, 1870.

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