

MAGNETIC RESONANCE IMAGING OF STEM CELL VIABILITY USING DUAL POSITIVE (T1) AND NEGATIVE (T2*) CONTRAST AGENTS IN A MOUSE BRAIN INJURY MODEL

Ethel Ngen¹, Yoshinori Kato¹, Wenlian Zhu¹, and Dmitri Artemov¹

¹Russell H. Morgan Department of Radiology and Radiological Sciences, ICMIC Program, Johns Hopkins University, School of Medicine, Baltimore, Maryland, United States

Introduction: In order to effectively manage stem cell-based therapeutic regimes, there is a need for non-invasive *in vivo* imaging strategies to track the integration and viability of transplanted stem cells. In this study we evaluate the ability of a novel MRI stem cell tracking technique to track the viability of transplanted stem cells *in vivo*.

Method: To achieve non-invasive monitoring of cell viability we used the MR contrast activation strategy previously tested with liposomal carriers (1). Basically, superparamagnetic iron oxide (SPIO) nanoparticles and gadolinium-diethylene triamine penta-acetic acid (Gd-DTPA) are coencapsulated within a carrier resulting in strong negative T2* contrast generated by the intact carrier. Dissociation of the carrier releases both contrast agents, and rapidly diffusing small GdDTPA chelates generate positive T1 MRI contrast around the core which contains relatively immobile SPIO nanoparticles. To extend this concept to magnetic cell labeling, human mesenchymal stem cells (HMSCs) were labeled with both high molecular weight, negative (T2*) and low molecular weight positive (T1) contrast agents: bionized nanoferrite particles (BNF) and Gd-DTPA respectively, and the cellular viability assessed (2-4). The cells were then implanted contra-laterally to a cerebral lesion, induced by single high-dose conformal irradiation (60 Gy) in the left cerebral hemisphere of both immunodeficient and immunocompetent mice, 2 days following injury (5). Both groups were monitored over a period of 20 days.

Results: In immunocompetent mice a T1-enhancement was observed around the HMSC administration site 2 h post-implantation and this increased over the next 5 days (Figure 1A (top)). However, no T1 enhancement was observed in the immunodeficient mice (Figure 1A (bottom)). This indicates that following graft rejection in immunocompetent mice, Gd-DTPA is released from the ruptured cells and diffuses away from the large BNF nanoparticles into the surrounding tissues generating a T1 enhancement. However, in live cells Gd-DTPA is in close proximity to BNF in intact cell compartments and the T2* effects of the BNF particles predominate. Furthermore, in immunodeficient mice areas with hypointense signals were observed towards the lesion site about 5 days post-implantation (Figure 1B (bottom)), while no significant signal enhancement was observed in the contralateral hemisphere in immunocompetent mice (Figure 1B (top)). This hypointense signal observed at the lesion site was attributed to migration of magnetically labeled viable HMSC.

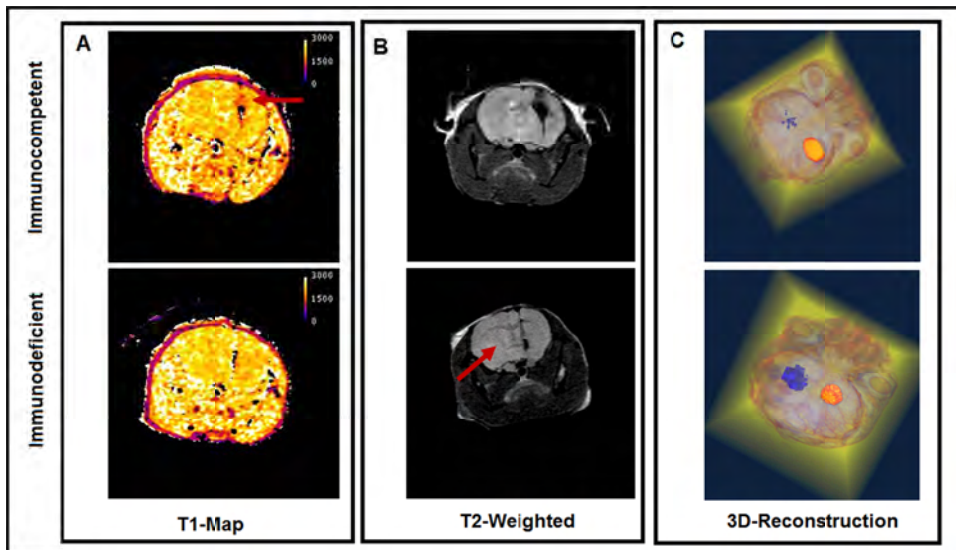


Figure 1. A) T1-maps of both immunocompetent and immunodeficient mice. The arrow indicates release of Gd-DTPA in immunocompetent mice at the HMSC administration site 24 h post administration. B) T2-weighted images of both immunocompetent and immunodeficient mice: the arrow indicates HMSC migration to lesion site 5 days post HMSC administration in immunodeficient mice. C) 3D reconstruction of T2*-weighted images of perfused mouse brains confirming the presence of HMSCs at the injection (orange) and the lesion (blue) sites.

Conclusion: These results suggest that the T2* and T1 signal changes in the surroundings of transplanted dual-labeled stem cells could be an effective and simple non-invasive method to track, stem cell migration and viability *in vivo*.

References:

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