Manganese Guided Cellular Magnetic Resonance Imaging Enables Evaluation of Human Stromal Cell Viability

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Background: Human stromal cells (hSC) have demonstrated restorative capabilities of the injured myocardium. Although iron oxide particles have demonstrated *in vivo* MRI cell tracking, fundamental biological properties including cell viability of transplanted cells are not evaluated. We tested the hypothesis that manganese chloride ($MnCl_2$) will enable MRI assessment of hSC viability.

Methods: Human stromal cells (Cognate, Sunnyvale, CA) were trypsinized and labeled with different concentrations of $MnCl_2$ in normal saline and incubated for 0.5-1.0 hour at 37°C and 5% CO_2. Biological properties of hSC were monitored by modulating the activity of calcium channels using verapamil (calcium channel antagonist). T_1 and T_2 mapping was performed at 0.01-3.00 mM of $MnCl_2$ solution with 1.5 T GE Excite whole-body MRI scanner (Signa, GE Medical Systems, Milwaukee, WI) with a 5-inch receive only surface coil. For T1 measurements, spin echo (SE) inversion recovery sequence (FOV 12 cm, matrix size of 128x128, TR 3000 ms and TE 50-2200 ms at 300 ms steps) were used. We made T2 measurements using SE sequence (FOV 12 cm, matrix size of 128x128, TR 2500 ms and TE 10-80 ms at 10 ms steps). Then the data were analyzed to extract T1 and T2 values through nonlinear least-square fits to the SE inversion recovery and the SE decay curve respectively. *In vitro* cellular MRI was performed using optimized SE sequence (FOV 12 cm, matrix size of 256x256, TR 800 ms and TE 3.4 ms). Modulation of hSC calcium channel activity by verapamil was assessed by measuring changes in signal intensity.

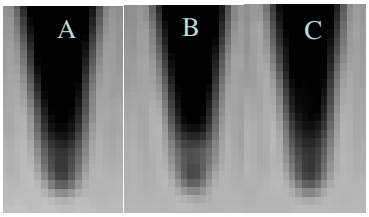


Figure 1

Figure 1: MRI of hSC in different Mn concentration (A) control (hSCs in normal saline), (B) 0.10 mM Mn, (C) 0.10mM with 250 μM Verapamil

Figure 2

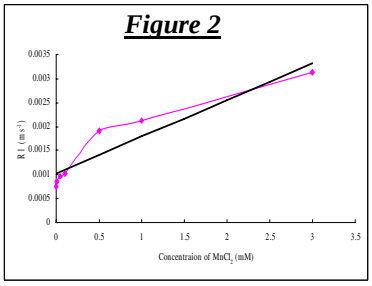
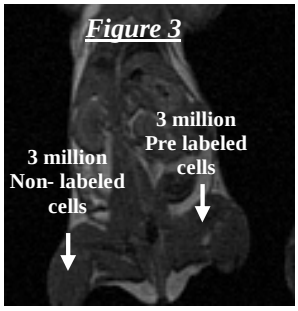


Figure 3



Results: *In vitro* assessment of cell viability was confirmed by increased signal intensity (SI) due to the T1-shortening effects of intracellular $MnCl_2$ accumulation. Viable hSC generated increased T1-shortening effects with increasing extracellular concentrations of $MnCl_2$. Calcium-channel mediated biological activity of hSC was confirmed by the significant 40% reduction of SI (858±50 vs. 524±48, $p<0.05$, n=3) when verapamil was co-administered with 0.10mM $MnCl_2$ (Figure 1). Furthermore, T1 and T2 relaxation times of Mn labeled hSC have been measured (Figure 2). Finally, *in vivo* MRI demonstrated viability of hSC following transplantation into mouse right hindlimb as shown in figure 3 (white arrow).

Conclusion: $MnCl_2$-guided cellular MRI demonstrates the potential to detect calcium-channel mediated biology of transplanted hSC including cell viability. This technique may enable MRI-guided biological evaluation of transplanted cells.

References: [1] Aoki I, et al. *NMR Biomed* 2006; 19(1):50-59. [2] Bruvold M et al, *Invest Radiol* 2005;40: 117-125.