Manganese--Enhanced MRI in the Evaluation of Cell-Based Therapy

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Background

To date, the underlying mechanism responsible for the restoration of the injured myocardium following transplantation of stem cells has not been clearly identified. Three major hypotheses have been previously proposed: cardiac differentiation of transplanted cells (de novo myocardial regeneration), paracrine effect on existing myocardium (myocardial salvage) or recruitment of cardiac progenitor cells (resident stem cells). Manganese-enhanced MRI (MEMRI) allows a reliable method of imaging viable myocardium. Utilizing MEMRI, we evaluated the changes in the viability of the injured myocardium to further investigate the underlying mechanism of functional restoration using stem cell therapy.

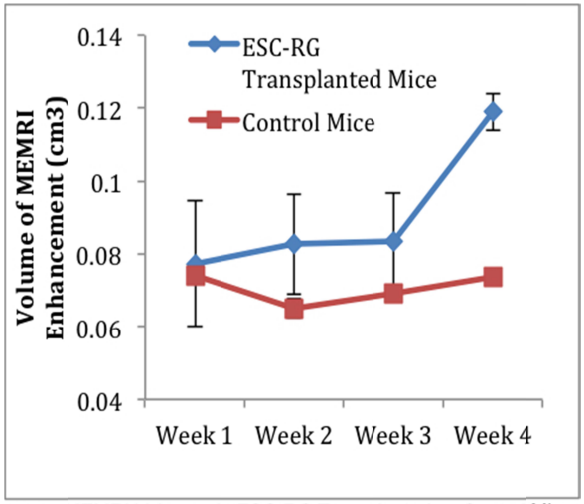

Fig 1. MEMRI Volumes in ESC-RG Transplanted vs Control Mice

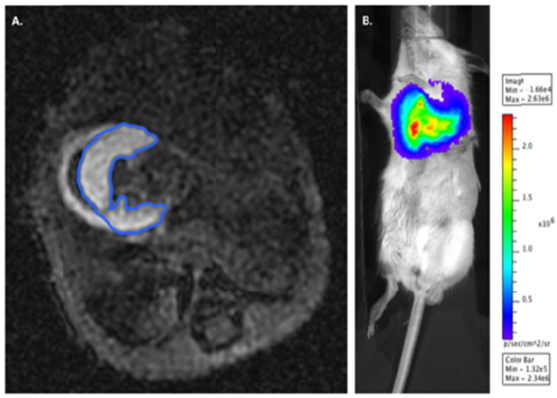

Fig 2. A) MEMRI enhancement of viable myocardium in an ESC-RG transplanted mouse B) BLI of transplanted ESC-RGs

Methods

Thirteen Fox Chase SCID Beige mice were subjected to permanent left anterior descending (LAD) ligation to create a mouse myocardial injury model. 2.5 x 10^5 reporter-gene transduced mouse embryonic stem cells (ESC-RGs) containing firefly luciferase (fluc) were transplanted into the intra-infarct region in 11 mice. Two mice were injected with normal saline into the intra-infarct region to serve as controls. 3T cardiac MRI was performed weekly for 4 weeks following LAD ligation and ESC-RGs transplantation to obtain LVEF measurements and MEMRI images. Additionally, bioluminescence images (BLI) were obtained weekly utilizing the transduced fluc gene to demonstrate persistent viability of the ESC-RGs. At weeks 2, 3 and 4, the hearts were explanted, sectioned along the short axis plane and processed for H&E staining. The H&E stained slides provided histological correlation of MEMRI and BLI.

Results

We demonstrate a trend towards improved LVEF with ESC-RGs transplanted hearts, consistent with the results of our group's previously published data. The control group, in contrast, demonstrates no functional improvement with a persistently depressed LVEF. A more sensitive measurement of myocardial restoration is significantly increased MEMRI signal observed in the ESC-RGs vs. control mice (.119±.005 cm3 vs .0736±.001 cm3 respectively, p=0.034), indicating improved myocardial viability (Figure 1). BLI confirmed the presence as well as engraftment of the transplanted ESC-RGs, which were confirmed histologically (Figure 2).

Conclusions

This study demonstrates the functional improvement in ESC-RG transplanted mice. In addition, MEMRI shows a significant increase in viable myocardium in ESC-RG transplanted hearts. This finding may support the hypothesis that functional restoration with stem cell therapy may be due to increased viability of the myocardium.