A Local Static Magnetic Field Confines Implanted Stem Cells in Targeted Regions and Improves Their Therapeutic Efficacy for Heart Failure

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Introduction

Cell therapy holds a great promise for curing of various degenerative diseases, including congestive heart failure (CHF). However, both animal and human studies showed very marginal benefits of cell therapy. Lack of strategies to confine implanted stem cells in a targeted region may underlie the limited efficacy observed in cell therapy. This study was to determine whether an externally applied static magnetic field (SMF) increase the retention of superparamagnetic iron oxide (SPIO)-labeled cells in a targeted organ and then improve efficacy of cell therapy.

Materials and Methods

Adipose-derived stem cells (ASC) were isolated from subcutaneous adipose tissue of male rats. The ASC were labeled with SPIO. Effects of SMF on proliferation, trans-differentiation and DNA integrity of the SPIO-labeled ASC (ASC_{SPIO}) were determined after one week of exposure of the ASC_{SPIO} to 0.5 Tesla SMF. CHF was induced on 26 female inbred Lewis rats by occlusion of the left anterior descending (LAD) coronary artery. Immediately after the LAD occlusion, the rats were randomly divided into three groups. Rats in group 1 (n = 5) were subjected to four intramyocardial injections of cell-culture medium (CCM, ~125 μL/injection) into the infarct rim. Animals in group 2 (N = 12) were subjected to 4 intramyocardial injections of the ASC_{SPIO} (~1.25 x 10^6/injection). The animals in group 3 were subjected to 4 injections of same number of ASC_{SPIO} and one-week subcutaneous implantation of a 1.0 cm diameter magnetic disc on the left chest wall. The magnet generated a ~0.1 Tesla SMF on the surface of the rat hearts. During four weeks of postoperative recovery, rat heart function was monitored in MRI. At end of the recovery, hearts were excised and the ASC_{SPIO} in the hearts were quantified using real-time polymerase chain reaction (RT-PCR).

Results

In our *ex vivo* cell study, MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrasodium bromide) assay showed that the level of formazan in ASC_{SPIO} subjected to a 0.5 Tesla SMF (98 ± 13%) was comparable to that of control ASC_{SPIO} (set as 100%) following one week of culture with an identical cell number at the beginning. This demonstrated that a SMF at 0.5 Tesla had no negative impacts on proliferation of the ASC_{SPIO}. In addition, it was found that both control ASC_{SPIO} and those subjected to one week of a 0.5T SMF had similar expressions of the markers specific to adipogenic, osteogenic, and chondrogenic differentiations following respective inductions. This indicates that a 0.5T SMF does not affect the differentiation potential of ASC_{SPIO}. In the Comet assay, we did not observe any ASC_{SPIO} with evident DNA fragmentation after one week of exposure to 0.5T SMF. In our *in vivo* study, it was found that the CHF hearts subjected to both ASC_{SPIO} and SMF (Group 3) contained significantly more ASC_{SPIO} (3.6 x 10^5 ± 1.0 x 10^4 ASC_{SPIO}/heart) than the hearts treated only with ASC_{SPIO} (Group 2, 1.9 x 10^5 ± 1.2 x 10^4 ASC_{SPIO}/heart) (Figure 1). As a result, cine MRI showed that left ventricular ejection fraction (LVEF) was significantly greater in group 3 (58 ± 5%) than in group 2 (49 ± 6%) (Figure 2). LVEF of the two groups were considerably greater than that of the CHF hearts treated with CCM (group 1, LVEF of 32 ± 4%) (Figure 2).

Discussion and Conclusion

Our study demonstrates that one week of exposure to SMF (0.5 Tesla) does not affect the proliferation, differentiation and DNA integrity of ASC_{SPIO}. Use of a SMF even at 0.1 Tesla significantly enhanced confinement of ASC_{SPIO} in the infarct hearts. Consequently, the infarct hearts treated with ASC_{SPIO} and SMF had a significantly improved recovery of LVEF compared to those treated only with ASC_{SPIO}. Therefore, we conclude that a local SMF can significantly improve therapeutic efficacy of stem cells.