Adipose-Derived Stem Cells Improve Global and Regional Function of the Infarct Hearts

G. Tian[1], L. Wang[1], B. Xiang[1], J. Wang[1], G. Li[1], M. Gruwel[1], M. Glogowski[1], T. Kashour[2], J. Rendell[1], B. Tomanek[1], R. Deslauriers[1], and J. Deng[1]

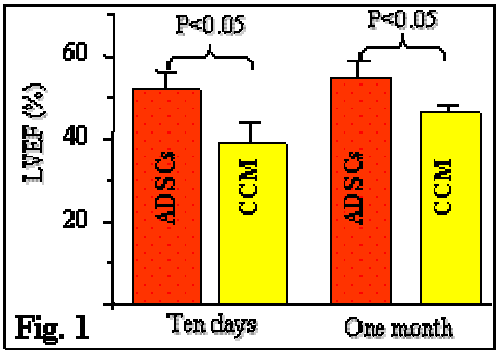
[1]Institute for Biodiagnostics, National Research Council Canada, Winnipeg, Manitoba, Canada, [2]Cardiology, St. Boniface General Hospital, Winnipeg, Manitoba, Canada

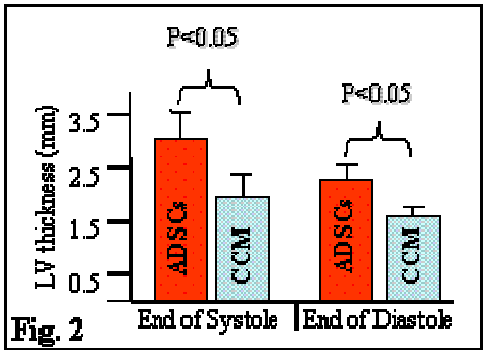
Introduction: The subcutaneous adipose (fat) tissue contains a population of cells that has been shown being able to differentiate into various cell types. Thus, the cells are called "adipose-derived stem cells (ADSCs)". The present study was to determine whether intra-myocardial injections of the ADSCs improved cardiac function of the infarct-failing hearts.

Materials and Methods: ADSCs were isolated from the subcutaneous adipose tissue in abdominal region of the inbred Lewis rats. The ADSCs were then labeled with super-paramagnetic iron oxide (SPIO) and Lenti-viral vector encoding a gene for green fluorescent protein (Lenti-GFP) for tracking the stem cells *in vivo* and *in vitro*, respectively. Fourteen inbred Lewis rats were divided into two groups (n = 7/group). Both groups of the animals underwent an open-chest surgery for a permanent occlusion of the left anterior descending (LAD) coronary artery. One week after the LAD occlusion, rats in group 1 received intra-myocardial injections of the labeled ADSCs (5-10 x 10^6) whereas those in group 2 received intra-myocardial injections of cell-culture medium and used as a control. The rats in both groups were then allowed to recover for four weeks, during which ADSCs engraftment and cardiac function were monitored using MR imaging. At the end of the recovery, the hearts were removed from animals for immunohistochemical assessments.

Results: We found that T_2 and T_2^* relaxation times of the labeled ADSCs were almost linearly related to cell concentration and passage (data not shown), suggesting that T_2/T_2* MR imaging are a sensitive technique to monitor the engraftment and proliferation of the injected ADSCs. Moreover, the grafted ADSCs appeared as a signal void region on MRI (panel A of Figure 3). In addition, cine MR imaging showed that the LV ejection fractions (LVEF) were significantly greater in group 1 than in group 2 at 10 days (52% ± 4% vs. 39% ± 5%) and 4 weeks (54% ± 2% vs. 47% ± 4%) after ADSC transplantation (Figure 1). Furthermore, wall thickness of infarct LV region measured at the ends of systole and diastole were significantly thicker in group 1 than in group 2 (Figure 2). Tissue sections obtained from the infarct region at the end of the protocol showed a perfect match of SPIO with GFP, suggesting that signal void regions on the MRI were living ADSCs.

Conclusion: Our results demonstrated that ADSCs can be effectively labeled with SPIO and Lentiviral-GFP. Engraftment and proliferation of the ADSCs can be monitored *in vivo* using T_2/T_2* MR imaging. ADSC transplantation improves global and regional function of infarct hearts and reduces infarction-associated cardiac remodeling. We therefore conclude that ADSCs are an effective cell source for cardiac repair.





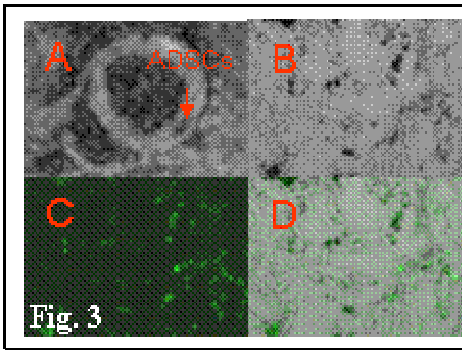


Figure 1. Comparison of LV ejection fraction (LVEF) between group 1 and group 2. Hearts in group 1 showed a significantly higher LVEF than those in group 2. This demonstrates that ADSCs improves global function of the infarct hearts. CCM, cell-culture medium.

Figure 2. Thickness of the infarct LV wall measured at the ends of systole and diastole. The hearts in group 1 had a significant thicker LV wall in infarct region than group 2 hearts did. Wall thickening was also greater in group 1 than in group 2, demonstrating that ADSCs improved regional function of the infarct hearts.

Figure 3. Panel A shows an *in vivo* MR image of a group-1 heart with a signal void region in the anterior wall of the LV. Panel B shows a tissue section obtained from the signal void region and stained for SPIO that appeared as black dots. Panel C shows a fluorescent picture of the panel B. The green dots were green fluorescent protein (GFP) expressed by the grafted ADSCs. Panel D is a superimposition of panels B and C, showing a perfect match of SPIO with GFP.