AAV SDF-1 AUGMENTED MYOBLAST THERAPY FOR CARDIAC FAILURE

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Introduction

During the past few years, cases of cardiac failure have increased as a result of improved therapy and survival of patients following myocardial infarction. In 2005 the estimated direct and indirect cost of Congestive Heart Failure (CHF) management in the United States alone is $27.9 billion. Currently there is no clinically approved modality of treatment to repair the underlying defect of ischemic injury. Our study involves induction of cardiac failure in rats by creating an ischemic injury. This is followed by human myoblast transplant and re-evaluation of cardiac function. The study also involves the administration of gene therapy using AAV SDF-1 (Stromal Derived Factor) to the myoblasts prior to transplant. SDF-1 and its receptor, CXCR4, are essential for cardiogenesis, hematopoiesis, and vasculogenesis during embryonic development. Expression of SDF-1 mRNA is observed in heart, brain, liver, and kidney. SDF-1 levels are significantly elevated post-ischemic injury. The modulation of SDF-1 levels post-ischemic injury may have a role in the repair and regeneration of the damaged myocardium. We hypothesize that increased levels of SDF-1 with myoblasts will drive stem cells from their niche to home into the myocardium and promote repair process.

Experimental

Myocardial infarction is created in 7-8 weeks old nude rats. 3 weeks post-infarct, cardiac gated MR imaging was performed. Superparamagnetic iron oxide (SPIO) labeled human myoblasts are injected with or without AAV-SDF-1 transduction. Cardiac MRI was performed on a 4.7 T Bruker Avance spectrometer using acquisition triggering at the peak of the R wave (SA instruments). Cell transplants were imaged using a Fast Low Angle Shot (FLASH) sequence (matrix= 256 x 192, TE = 2.7 msec, FOV = 40 mm x 30 mm, thickness = 1 mm). Pulse repetition time (TR) was dependent on the R–R interval (~200 ms). MRI was performed at 3 weeks post-infarction, 1 week, 4 weeks and 8 weeks post-transplant. Control animals receiving non-transduced myoblasts transplants were also imaged using the same MRI protocol. The images are analyzed using CAAS MRV software from Pie Medical Imaging (Netherlands). End-diastolic and end-systolic volumes are used to calculate ejection fraction, stroke volume, and cardiac output. The software also analyzes regional wall mobility to evaluate improvements post-transplant.

Results and Discussion

From the preliminary results we have been able successfully deliver and transplant human myoblasts in the nude rats post-infarction. The SPIO labeled cells were able to be tracked till the end of the study (8weeks post-transplantation). The cardiac output improved 8 weeks post-myoblast transplant. The cardiac output increased from the 3 week post-infarct value of 46.12% to 77.59%. The regional wall mobility also improved as shown in figure 2 below.

Figure 1 below shows the Feridex labeled myoblasts transplanted into the border of infarct in the left ventricle. Figure 2 below shows the recovery of function after 8 weeks in an ischemic model of cardiac failure following transplant of SDF transduced myoblasts.

Conclusions

We were able to efficiently track SPIO labeled cells post-transplant and accurately evaluate cardiac function using MRI.

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