

GATA4, A DOUBLE BLADED SWORD FOR CARDIAC REPAIR

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Introduction: Therapeutic efficacy of bone marrow mesenchymal stem cells (MSCs) to treat myocardial infarction needs to be enhanced due to their limited cardiomyogenic ability. Transcription factor GATA4 plays a pivotal role near the top of the cascade of events that lead to cardiac differentiation. Based on our recent findings, direct injection of engineered cardiac fibroblasts expressing GATA4 fused with cell penetrating peptide VP22 into the peri-infarct zone provided an efficacious strategy to treat ischemic cardiomyopathy leading to increased expression of cardiac myosin heavy chain and decreased collagen deposition. We have similarly demonstrated that the delivery of SDF-1 to the heart soon after myocardial infarction (MI) leads to stem cell recruitment and preservation of cardiac myocytes. We hypothesized that by combining VP22:GATA4 and SDF-1 delivery to the myocardium we could recruit stem cells to the heart and force their differentiation following MI.

Methods: In Lewis rat model, MSCs isolated from bone marrow and stably transduced with Lentiviral VP22:GATA4 or SDF-1 were infused one week after LAD ligation. Experimental groups consisted of Saline, Control MSC, SDF-1 MSC, VP22:GATA4 MSC or combined VP22:GATA4 and SDF-1 MSC. In each situation 2 million MSC were infused, but no more than 1 million of any specific genetically modified MSC was infused. Ejection fraction was quantified by echocardiography 2 and 6 weeks after MI. And TUNEL assay was performed 4 days after cell infusion.

Results: At 2 w after MI we observed a $23 \pm 1\%$ and $40 \pm 5\%$ improvements in ejection fraction in SDF-1 group relative to saline controls. We observed a $23 \pm 4\%$ decline in function in the VP22:GATA4 group and no improvement in the combination group. At 6 weeks after MI, we observed no significant improvements in the MSC group and a $47 \pm 10\%$ and $20 \pm 4\%$ improvements in the SDF-1 and combo groups, the function in the VP22:GATA4 group improved to have no significant difference compared to saline control. Furthermore, we observed over expression of GATA4 within the infarct zone via the infusion of VP22:GATA4 MSC led to a significant increase in the number of TUNEL-positive cardiac myocytes nuclei, while SDF-1MSC led to a significant decrease in the number of TUNEL-positive cardiac myocytes compared with MSC control.

Conclusions: Intravenous infusion of MSC can be used to deliver natural and chimeric proteins to the myocardial tissue following MI. The initial increased apoptotic cardiomyocytes in the peri-infarct zone followed by declined cardiac function in those animals that received VP22:GATA4 MSC suggest that forced induction of cardiac differentiation soon after MI may have detrimental effects on myocardial tissue leading to increased cardiac myocyte death and adverse remodeling. Timing of transcription factor activation to induce myocardial regeneration may be crucial to develop an efficacious strategy to treat MI.