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**Human iPSC-derived cardiomyocytes preserve murine heart function after myocardial infarction unlike adipose tissue-derived stromal cells**

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**INTRODUCTION:** Despite progress in pharmacological treatment of myocardial infarction (MI), there is still an immense need for novel therapies for this life-threatening condition. Accordingly, cell-based therapies have been extensively investigated with most studies focusing on mesenchymal stromal cells. However due to their inability to differentiate into cardiomyocytes as well as limited survival upon in vivo administration, no effective treatment of MI has been developed. In contrast, application of hiPSC-derived cardiomyocytes (hiPSC-CM) represent biologically rational approach with pre-clinical studies confirming their therapeutic potential in various models of MI. However further optimization is required due to limited survival of hiPSC-CM upon in vivo administration. Therefore, we evaluated the therapeutic potential of genetically modified hiPSC-CM in murine model of acute MI and compared it to the effect of adipose tissue-derived stromal cells (ADSC).

**METHODS:** In the first step hiPSC overexpressing GFP, luciferase (Luc) and pro-angiogenic and cardioprotective factors: heme oxygenase-1 (HO-1, heme degrading enzyme) or stromal cell-derived factor-1 (SDF-1, pro-angiogenic chemokine) were subjected to cardiac differentiation which yielded in each group 70-90% cardiac troponin T-positive contracting cells. hiPSC-CM (5x10⁵ in 10 µl) were administered into NOD-SCID mice which underwent permanent ligation of left anterior descending (LAD) coronary artery. The cells were injected into the peri-infarct zone. Mice subjected to sham operation as well as injected with saline after MI were used as controls. The ultrasonography of hearts was performed on day 7, 14, 28 and 42 whereas the presence of hiPSC-CM was monitored using IVIS Spectrum system upon administration of luciferin and analysed in sections of collected hearts. The same experimental scheme was used to assess therapeutic potential of ADSC (CD105+CD73+CD90+CD44+CD146-CD34-) overexpressing luciferase and GFP.

**RESULTS:** Ultrasonography demonstrated that upon delivery of hiPSC-CM the left ventricle ejection fraction (LVEF) was very significantly higher in comparison to control group injected with saline after induction of MI. In contrast, no improvement of LVEF was observed after administration of ADSC. Interestingly, measurements of luciferase activity revealed the strongest bioluminescent signal in the hearts of mice transplanted with iPSC-CM-HO1 42 days after MI. Importantly, the survival of hiPSC-CM in murine myocardium six weeks upon administration was further confirmed with immunofluorescent analysis of heart sections using human specific anti-Ku80 antibody. Again, luciferase activity was not observed upon delivery of ADSC.

**CONCLUSION:** These results strongly indicate that administration of hiPSC-CM, unlike ADSC, preserve murine heart function in acute MI model. Additionally, overexpression of HO-1 may positively influence their survival upon in vivo delivery into infarcted tissue.
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