Co-transplantation of mesenchymal bone-marrow cells increases persistence of murine iPS-derived cardiomyocytes at 24h after intramyocardial injection into healthy syngeneic hearts

M. Maaß¹, B. Krausgrill¹, C. Steigerwald¹, K. Urban¹, A. Fatima², M. Halbach¹, D. Ladage¹, J. Hescheler², T. Saric², J. Müller-Ehmsen¹

Abstract

Objectives:

Cardiac cell replacement therapy is a promising therapy to improve cardiac function in heart failure, a major cause of morbidity and mortality in the world. In contrast to clinically intensively tested bone-marrow cells, embryonic or induced pluripotent stem cell can be differentiated into functional cardiomyocytes (ES-CM or iPS-CM) which after transplantation can integrate into host myocardium and thereby replace lost myocardium. Since engraftment and persistence of transplanted ES-CM and iPS-CM was found to be very limited, we tried to increase it in this study by co-transplantation of non-cardiomyocytes with iPS-CM.

Methods:

ES-CM and iPS-CM were derived and highly purified from transgenic male murine embryonic or induced pluripotent stem cells using an antibiotic resistance under the control of a cardiac specific promoter. 300,000 ES-CM or iPS-CM with or without admixture of 300,000 syngeneic male murine mesenchymal stem cells (MSC) or syngeneic male murine embryonic fibroblasts (MEF) were intramyocardially injected into healthy hearts of syngeneic female mice. Hearts were explanted after 24h, DNA was isolated and the number of transplanted cells was determined using quantitative real-time PCR with transgene specific primers. For every surgery day, 1 additional aliquot was mixed with an explanted heart ex-vivo and served as control and known dilutions of transgene positive in transgene negative DNA were included to derive a calibration curve.

Results:

24h after intramyocardial injection of iPS-CM, we detected 0.62±0.44% of the transplanted cell number (approx. 1900 cells), which was significantly less than in the surgery day controls (p < 0.001) and similar to the intramyocardial injection of ES-CM with 0.93±0.28% (approx. 2800 cells). After co-transplantation of MSC numbers were 2.5-fold higher with 1.54±0.23% of transplanted transgenic cells (p < 0.05 vs. iPS-CM, approx. 4600 cells). Preliminary data suggest that co-transplantation of MEF showed similar results with 1.74±0.93% or approx. 5200 cells).

Conclusions:

Persistence of iPS-derived cardiomyocytes at 24 hours after intramyocardial injection is increased by co-transplantation of MSC, but it remains very limited. Nevertheless, this strategy could be useful to improve the efficiency of cardiac cell replacement therapy and should therefore be further investigated.