Embedment of highly purified murine iPS-derived cardiomyocytes in biodegradable macroporous microspheres as microcarriers facilitates intramyocardial injection of huge absolute cell numbers without altering low fractional cell engraftment

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Abstract

Objectives:

Heart failure is a major cause of morbidity and mortality in the world and cardiac cell replacement therapy is a promising strategy to restore cardiac function in heart failure. Since functional cardiomyocytes are the lacking cells in heart failure, iPS-derived cardiomyocytes (iPS-CM) are good candidates for transplantation. However, engraftment efficiency is very limited for purified iPS-CM and the small volumes suitable for intramyocardial injection in mice limits the absolute number of transplanted cells. Therefore, we tested embedment of purified murine iPS-CM in biodegradable macroporous microspheres as microcarriers for intramyocardial injection.

Methods:

Male murine Acta2-iPS expressing an antibiotic resistance and eGFP under the control of the Acta2-promotor were differentiated to Acta2-iPS-CM in hanging drops and highly purified with respective antibiotic treatment. Prepared single cell suspensions were either used directly for intramyocardial injections (iPS-CM alone) or they were cocultured with biodegradable macroporous microspheres and the loaded microcarriers were intramyocardially injected (iPS-CM in microspheres). Healthy syngeneic female mice served as recipients in an open chest surgery with 2 intramyocardial injections of 10µl each. Hearts were excised immediately after surgery (0h) or after 24h, genomic DNA was prepared and the number of persisting transplanted cells was determined using quantitative real-time PCR with y-chromosome specific primers.

Results:

After optimization, embedment of iPS-CM in microspheres was very efficient and loaded microspheres were not destroyed or lost when passed through the injection needle. Preliminary data suggest that immediately after intramyocardial injection of iPS-CM alone, only 14.6±5.9% of injected cells were detectable and this value further declined to 2.5±0.8% at 24h. Similarly, after intramyocardial injection of iPS-CM in microspheres numbers were 12.6±4.0% at 0h and 1.4±0.7% at 24h (both P=n.s. vs. iPS-CM alone). Absolute numbers were significantly higher in iPS-CM in microspheres than in iPS-CM alone in controls and at both time points studied, and the difference was 4-5-fold in controls and at 0h and declined to 2.5-fold at 24h.

Conclusions:

Embedment of highly purified murine iPS-derived cardiomyocytes in biodegradable macroporous microspheres as microcarriers is feasible and facilitates intramyocardial injection of huge absolute cell numbers without altering low fractional cell engraftment. Thus, this strategy could be useful to enable efficient cardiac cell replacement therapy.