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Long-term functional benefits of human embryonic stem cell-derived cardiac progenitors embedded into a fibrin scaffold.

Bellamy V[1], Vanneaux V[2], Bel A[3], Nemetalla H[4], Emmanuelle Boitard S[5], Farouz Y[1], Joanne P[5], Perier MC[1], Robidel E[1], Mandet C[1], Hagège A[4], Bruneval P[6], Larghero J[2], Agbulut O[5], Menasché P[7].
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Bellamy et al. investigated the long-term therapeutic effects of human embryonic stem cell derived cardiac progenitor cells (SSEA-1$^+$) in a rodent myocardial infarction model. Eighty immune deficient rats underwent coronary artery ligation, followed by implantation of either cell-free fibrin patch (n=25) or a fibrin patch loaded with hESC-derived cardiac progenitor cells (SSEA-1$^+$ progenitors n=700000/patch). A sham-operated group served as a control. During 4 months of follow-up, left ventricular function was assessed by echocardiography. They found, compared to baseline, a stable LVEF in the sham group, a slightly increase of LVEF in fibrin group and the largest improvement in the fibrin-progenitor cell group. Similar results were observed for LV end-diastolic volume (LVEDV) and LV end systolic volume (LVESV). Furthermore, angiogenesis in the infarction border zone and results from a 5- component heart failure score were significantly improved in cell-fibrin group, compared to sham group. No teratoma formation was observed in any of the animals during follow-up. Surprisingly, engrafted progenitor cells were only detected shortly after transplantation, and already 7 days after implantation no grafted cells were identified in immunohistochemical analysis and PCR. Bellamy et al. conclude that implantation of a fibrin scaffold with ESC-derived cardiac progenitor cells results in sustained improvement of contractile properties and attenuation of remodeling without sustained donor cell engraftment. As a possible mechanism for the beneficial effects of progenitor cells in their study, they see the paracrine effects on innate reparative processes.

Due to the fact, that already seven days after implantation, no engrafted cells could be observed any more, it is obvious that the functional benefits, demonstrated in this study, do not result from remuscularization of the infarction area. Most likely, cell-induced paracrine effects, initiating signaling cascades, leading to improved angiogenesis and reduced fibrosis account for the observed therapeutic effect. To achieve those local paracrine effects, the use of cell loaded fibrin scaffolds might represent an effective method, as it reduces the initial cell washout, compared to direct cell injection. The initially high cell concentration in the infarction region might account for the demonstrated beneficial effects with a relatively low number of implanted cells (700000/patch).

Those undoubted beneficial paracrine effects might contribute to a slight improvement of left ventricular contractile function after a myocardial infarction of limited size, but most likely will not

be able to support failing hearts. Here the formation of a relevant mass of new myocardium is necessary.

Due to recent progress in stem-cell biology, differentiation of cardiomyocytes from hESC- or hiPSC in nearly unlimited numbers has become a reality. Those cardiomyocytes have been used in different cardiac repair approaches, by either- direct intramyocardial cell injection or transplantation after creation of engineered heart tissue (EHT) patches, in small animal models and a non-human primate study (1-4).

In contrast to the findings with cardiac progenitor cells by Bellamy et al., Chong et al (1) published data from a non-human primate myocardial infarction study. They demonstrated, that hESC derived cardiomyocytes survive during follow-up period of up to 3 months after intramyocardial cell injection and can remuscularize substantial amounts of the infarcted primate heart. Furthermore, they have shown electrical coupling between hESC cardiomyocytes and host myocardium by GCaMP3 signaling, but as a downstream of electrical coupling, they also detected ventricular arrhythmias in all animals. However, limitations of this study were the small animal number, the lack of functional investigations and no data are provided on how many of the initially injected cells (1billion per animal) survived during follow-up period. In line with the findings of Chong et al, we have shown in our own observations, published in abstract form, that relevant amounts of human iPS-cell derived cardiomyocytes survived the follow-up period of 4 weeks after EHT transplantation in a guinea pig infarction model. Furthermore, compared to a control group receiving cell free fibrin constructs, significant improvement of cardiac function was observed (5). Before cell therapies with hiPSC- or hESC-derived cardiomyocytes can be implemented as a clinical routine procedure, several unacknowledged questions need to be addressed. On the one hand, safety of the cells remains an important issue. Pluripotent cells carry out a risk for teratoma formation and additionally, the application of hiPSCs is associated with the risk of chromosome instability and mutations leading to malignancy. Therefore, strict testing of the cells is essential before clinical application.

Furthermore, the ideal cell delivery method remains undefined yet. The direct intramyocardial cell injection represents a simple method, however limited by the high number of cells needed and the high washout rate, especially when transplanting cells with pluripotent potential and risk for teratoma formation. On the other hand, there is the possibility to create in-vitro fabricated three-dimensional engineered heart tissue patches. However here, the graft thickness is still limited by the biologic diffusion capacity (50–200 µm), and reliable concepts for in-vitro as well as in-vivo vascularization are necessary to enlarge the graft thickness.

From an immunologic point of view, the use of hiPSC-derived cardiomyocytes theoretically allows for an autologous approach. However, this autologous solution is time-consuming and would need at least 6 to 9 months for generation of a patient-specific cardiomyocyte patch. Enormous logistic and economic hurdles would have to be overcome, as each iPSC cell-line is, from a regulatory board view, a new product. A more realistic scenario might be a bank of different iPSC or ESC

lines, with human leukocyte antigen–matched cells, requiring only a minimal immunosuppressive regimen.

Literature:

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Review provided by:

Simon Pecha, MD
University Heart Center Hamburg
Hamburg, Germany
s.pecha@uke.de

Simon Pecha, MD, is a Cardiac Surgeon at University Heart Center Hamburg and leads a Research Group for Myocardial Tissue Engineering at Cardiovascular Research Center Hamburg. He is member of the ISHLT BSTR Council and received the ISHLT Philip K. Caves Award in 2015.