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Commentary

Perspectives on the Evolution of Stem Cell Therapy for Heart Failure

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The advent of stem cell and cell-based therapy has opened the door to a non-pharmacological treatment of heart failure (HF). This exciting opportunity is at an early stage and many issues regarding optimization of this approach remain. A variety of stem cells (SCs), doses, and delivery methods are being tested in clinical trials, supporting the conclusion that there is still "no consensus on … which cell type to transplant, to improve efficacy and safety" (Silvestre and Menasché, 2015). To provide a guide going forward, Silvestre and Menasché take us through the evolution of the therapeutic use of SCs for heart failure (Silvestre and Menasché, 2015). Their main proposal is that "cardiac-committed cells" in general and "pluripotent stem cell-derived cardiac progenitors" in particular are "particularly attractive" candidates for cell therapy.

Many clinical trials have suggested SC efficacy. While early trials have focused on attempting to show improvements in morphologic measures such as left ventricular ejection fraction (LVEF), end diastolic volume (LVEDV), end systolic volume (LVESV), ventricular mass and scar size, others have attempted to examine surrogate clinical endpoints such as 6-min walk distance and Minnesota Living with Heart Failure scores. To adequately address which cell type is superior, direct cell-to-cell comparisons in pre-clinical studies on large animals and in clinical trials are needed. To date, numerous clinical and pre-clinical studies illustrate the therapeutic benefits of mesenchymal stem cells (MSCs), regardless of their tissue source. For example, in the TAC-HFT trial, MSCs improved cardiac function in chronic ischemic cardiomyopathy equal to or better than BM-mononuclear cells (Heldman et al., 2014). The POSEIDON clinical trial compared intra-myocardial injection of autologous and allogeneic bone marrow-derived (BM-) MSCs, and demonstrated a significant reduction in LVEDV in the allogeneic group (Hare et al., 2009). Unexpectedly, there appears to be an inverse relationship between cell number (20 million vs. 200 million) and therapeutic efficacy. Furthermore, analysis of patients from the POSEIDON-DCM and TRIDENT trials showed that intracardiac administration of allogeneic, but not autologous MSCs improved endothelial function 3 months after treatment (Premer et al., 2015).

The patient population and their different types of HF complicate the ongoing search for the best stem cell to improve cardiac function. Most studies have focused on ischemic cardiomyopathy; however, acute and chronic diseases do not necessarily respond similarly to a given cell type. Therefore it is not ideal to target one cell line and call it "the best". Instead it may be more advantageous for us to ask the question: are the parameters we focus on, such as EF, the best predictor of future morbidity and mortality? Many factors play a role in global EF; therefore segmental changes in EF may provide a better correlation with clinical outcomes. Clinical trials that have failed to produce the best results with respect to EF nevertheless improved quality of life as indicated by improvements in the Minnesota Living with Heart Failure score and the 6-min walk test (Sanina and Hare, 2015).

Silvestre and Menasché propose that cardiac-committed cells are superior therapeutically. However, in direct comparisons between MSCs and either induced pluripotent cell-derived cardiomyocytes (Weil et al., 2015) (iPSC-CM) or cardiosphere-derived cells (CDCs) (Li et al., 2012), MSCs provided equal cardiac functional improvements compared with both of these "cardiogenic" cell types except that MSCs were less effective at scar size reduction. Future therapies may be best served by combining cells. Recent studies show that the combination of c-kit + cardiac stem cells (CSCs) with either MSCs (Karantalis et al., 2015; Williams et al., 2013) or CDCs (Li et al., 2012) is more effective at restoring cardiac function than CSCs (Williams et al., 2013) or MSCs (Karantalis et al., 2015; Williams et al., 2013) alone in pig models of HF. In a recent murine study, Quijada et al. showed that a fusion of CSCs with MSCs was superior to the individual cells in improving left ventricular function and structure (Quijada et al., 2015). Perhaps cardiogenic cells are superior, and this property is manifested when they are combined with another cell type. Another approach is to pre-incubate or co-inject cytokines (or other factors) with cells.

Regardless of the cell type or injection route, SCs exhibit limited engraftment in the heart, suggesting that much of their effect is due to their paracrine release of growth factors, mitochondria, and/or exosomes. Silvestre and Menasché suggest that allogeneic cells are superior "biofactories" compared with autologous cells and produce higher levels of (or better) paracrine factors. Therefore, the milieu from which the cell is isolated may promote favorable interactions and prime cells to increase their production of growth factor(s), a property that may be more important than the type of cell used. The use of

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stem cells therapeutically is still at an investigational stage and many of these questions will remain unanswered until rigorous head to head clinical trials are performed with clinical outcomes.

Disclosures

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