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Cell Based Regenerative Therapy of Heart Failure: Where Do We Stand?

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Heart failure is a leading cause of death, responsible for an estimated 300,000 deaths in USA and 7.2 million deaths globally each year. Cell based regenerative therapy has been widely touted to have tremendous potential to repair damaged heart due to myocardial infarction, chemotherapy mediated damages, or other injuries leading to heart failure [1,2]. Various cell populations such as bone marrow hematopoietic stem cells, embryonic stem cell derived cardiomyocytes, cord blood stem cells, adult mesenchymal stem cells, hematopoietic (CD34+) stem cells in the peripheral blood, cardiac progenitors, adult cardiac stem cells, induced pluripotent stem cell derived cardiomyocytes/cardiac progenitors and transdifferentiated cardiomyocytes from endogenous cardiac fibroblasts have been suggested as a source of cells for replacement therapy [2-10]. This editorial aims to summarize the latest developments on the cell based regenerative therapy of heart failures, problems encountered and the challenges that need to be overcome for an effective therapy of heart failure.

Although the stem cell therapy of the heart with autologous stem cells has attracted a lot of attention, the emerging results are disappointing in that early-phase clinical trials that use patient' own stem cells show highly controversial outcomes. The trials identified as unflawed, according to a report in British Medical Journal (Br.Med.J. 348,g2688 (2014)), showed an effect size of zero [11,12] while only trials containing flaws showed positive outcomes [12]. However, currently there are three ongoing Phase 3 clinical trials that involve bone marrow derived cells. In the "BAMI" study (The Effect of Intracoronary Reinfusion of Bone Marrow-derived Mononuclear Cells (BM-MNC) on All Cause Mortality in Acute Myocardial Infarction) that currently recruits patients in Europe, the patients will be receiving autologous bone marrow derived mononuclear cells. In CHART-1 study (Safety and Efficacy of Autologous Cardiopoietic Cells for Treatment of Ischemic Heart Failure) sponsored by Celyad (formerly named Cardio3 Biosciences) that is ongoing but doesn't recruit patients currently in Europe, the patients will be receiving bone marrow derived mesenchymal stem cells. In the congestive heart failure study sponsored by Teva Pharmaceutical Industries, the patients will be receiving the bone marrow derived mesenchymal precursor cells, called CEP-41750 collected from different donors. The results from each of these 3 ongoing trails are expected in the next one to two years and will conclude whether the adult stem cells are optimal cell types towards the therapy of heart failure. Although adult stem cells offer an elegant autologous option, their ability to regenerate the myocardium seems to be limited. It is believed that the transplanted/injected adult stem cells release soluble paracrine factors that mediate cardiac repair and regeneration.

The other cell types that hold great potential for the treatment of heart failure are the induced Pluripotent Stem Cell (iPSC) derived cardiomyocytes/cardiac progenitors and the cardiomyocytes trans differentiated from dermal or cardiac fibroblasts. Although the iPSC technology is conceptually promising towards the therapy of heart failure especially in that billions of cardiomyocytes could be obtained from iPSC sources, there are several major roadblocks that need to be overcome before their application in clinical settings. Dedifferentiation of adult differentiated cells (skin cells or blood cells) to reprogram back to pluripotent (iPSC) state and the cardiac differentiation protocols are time consuming and laborious. The other concerns include cardiac differentiation leading to heterogeneous mixture of other clinically irrelevant cell phenotypes, teratoma formation, immunological rejection, electrical uncoupling on grafting with native cardiomyocytes and poor mechanical integration on the victimized site due the mechanical movement of the adjacent native cardiomyocytes especially in the left ventricles (the principal victimized site responsible for most sudden cardiac deaths in human) [7]. A recent study shows that intra-myocardial delivery of 1 billion human embryonic stem cell derived cardiomyocytes (hESC-CM) in a non-human primate model of myocardial ischemia-reperfusion led to significant remuscularization of the infracted heart [13]. But, the transplanted hESC-CM created an arrhythmogenic substrate and all the monkeys that received hESC-CM displayed arrhythmias. Further, the transplanted hESC-CM showed incomplete maturation over a 3-months period. Efforts to sort atrial and ventricular chamber specific ESC/iPSC-CM subtypes and to improve the maturation characteristics of these cardiomyocytes so as to create a more homogeneous phenotype that closely recapitulates the electrophysiological characteristics and pharmacological response of native cells are critically needed. These efforts should greatly enhance the safety of regenerative approaches designed to restore function to damaged or otherwise failing hearts in that it would minimize the possibility of potential arrhythmic complications.

One very promising approach for overcoming the disadvantages of ESC- or iPSC-based cell therapy of heart failure is offered by the trans differentiation (direct conversion) approach of converting one different cell type to another one by induction of some master genes in the source cells. This approach has been successfully demonstrated by the transdifferentiation of cardiac and dermal fibroblasts into cardiac cells in human and mice [14-16]. The cardiac fibroblasts within the scar tissue in the infarcted heart could be reprogrammed to cardiac fate with the right combination of cardiogenic factors thereby enabling the endogenous repair of the failing hearts. These advances hold promise for the possibility of a safer therapy for degenerative heart disease via transdifferentiation of the patients' own dermal or cardiac fibroblasts into functional cardiomyocytes. This approach will overcome several limitations of the existing approaches based on human ESC or human iPSC. The main advantage offered by the transdifferentiation methodology compared to the ESC and iPSC approaches is the prospect to transdifferentiate

fibroblasts without passing through the stage of pluripotency which is associated with a tumorigenic potential. However, this approach is still in its infancy at this time point and needs further experimental exploration to determine its candidacy for the cell based regenerative therapy of heart failure. Also, transdifferentiation efficiency and reproducibility are often controversial subjects across laboratories. Efforts to increase the transdifferentiation efficiency and reproducibility are critically needed prior to evaluating the therapeutic potential of transdiffferentiated cardiomyocytes in clinical settings.

In summary, a lot of hope is there for a safe and effective cell replacement therapy for patients with heart failure, but more efforts and time are needed to turn this hope into reality.

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