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Editorial

IPS Cells and Cardiac Diseases: Challenges Versus Promises

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Abstract

There is a lot of excitement about the use of stem cells as a treatment for cardiovascular disease. While there is great potential for stem cells in the treatment of heart failure and myocardial infarction, using stem cells for the treatment of congenital heart disease seems much more complicated. Today, stem cells are more suitably used for disease modeling and drug discovery than treatment of congenital heart disease problems.

Keywords: Stem cells; Cardiovascular disease; Congenital heart disease; Heart failure

Editorial

For the best part of the last decade, ever since the iPS cells were created in 2006 [1], the stem cell field has been blossoming. And at the heart of this scientific revival has been the heart itself. In the USA, 1 of every 4 deaths is attributed to heart disease [2]. The burden of cardiovascular illness is astounding, with as much as 300 Billion dollars per year being spent on treating this condition [3]. It comes as no surprise, then, that a huge push is being made for the use of stem cells to treat cardiovascular disease (CVD).

While the scientific and medical communities are aggressively pursuing stem cells as a treatment for Heart Failure (HF) and Myocardial Infarction (MI), other forms of CVD have been left behind, namely, Congenital Heart Disease (CHD). Admittedly, the burden of CHD is less than that of HF/MI [4], and the research being done in the latter field can certainly shed light on the use of stem cells in CHD.

Several issues arise when considering the use of stem cells as a treatment for CVD. The most significant of these problems has been identifying a good source of stem cells to use. Indeed, researchers have attempted to use bone marrow derived stem cells, skeletal muscle progenitor cells, human Embryonic Stem cells (hES), induced Pluripotent Stem cells (iPS), cardiac progenitor cells, endothelial progenitor cells, adipose tissue stem cells, amniotic stem cells, and much more [5-7]. The types of cells that have been the most rigorously studied, however, have been the hES, the iPS, the resident cardiac progenitor cells, and the bone marrow derived progenitor cells.

Different cell types present the researchers with different challenges. HES cells are the most undifferentiated cells, and can therefore, theoretically, be manipulated to differentiate into any cell type– including any of the 3 different cell types in the heart – myocardium, epicardium, and endocardium. And while this is a big advantage over other cell types, the "naïve" state of these hES cells is a double-edged sword. Indeed, studies have shown that injection of these cells post MI improved cardiac function, but they did so at a risk of the formation of teratomas in the pericardium [8]. Another issue with hES cells is their controversial embryological origin and a concern for immunological reaction following introduction of the foreign cells into the body of a patient.

iPS cells are able to navigate clear of several of these issues. Because iPS cells can be derived from patient specific fibroblasts, they raise no ethical or immunological problems. However, being very similar to hES in their undifferentiated nature, iPS cells also share hES cells' ability to form teratomas after implantation [7].

One cell type that does not confer a risk for teratoma formation is the population of endogenous cardiac progenitor cells. The discovery that the heart maintains a small population of progenitor cells that are able to multiply has allowed scientists to explore the option of using cardiac specific stem cells to treat CVD [9]. Two options are available for using these cell types; they can be harvested from the heart, programed *in-vitro*, and reintroduced into the heart, or they can simply be induced to differentiate *in-vivo*. As with other cell types, several problems arise when considering the use of resident cardiac progenitor cells. The first is the limited number of these cells [10], the second is the identification of the best cardiac progenitor cell to use. The fact that around half a dozen different cardiac progenitor cell phenotypes exist make the choice of the most appropriate cell a difficult one [6,10].

Scientists have also attempted to use bone marrow derived cells to treat CVD. The advantage of using the bone marrow is that unlike the heart, it has plenty of stem cells. And although clinical studies using bone marrow derived stem cells have shown improvement in cardiac function, this improvement has been modest [5,7]. Further research has shown that bone marrow stem cells introduced into the myocardium are not able to trans-differentiate into cardiomyocytes [3].

Another issue that arises when considering the use of stem cells for the treatment of CVD is the method of introduction of the stem cells. In essence, the options are either to introduce the stem cells into the heart as cells, or to perform tissue engineering using stem cells outside the heart, and instead of cells, scientists can then introduce a

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preformed tissue into the heart.

When considering the introduction of stem cells as individual cells into the heart, several options have been studied. One can inject them directly into the cardiac muscle, introduce them into the coronary circulation, or more simply, introduce them into the peripheral circulation [7]. Though no review has been done to compare the different methods, studies using all 3 methods have claimed an improvement in heart function after stem cell introduction [11-13].

The other option available is the use of scaffold material to provide a matrix into which stem cells are injected in vitro and allowed to grow, with the resulting tissue then implanted into the heart. Another alternative for tissue engineering is the injection of stem cell in a gel like solution directly into the heart. Here, the gel like solution acts as a biomatrix within the heart, allowing the process of tissue engineering to occur *in situ*. Moreover, researchers are also looking into the possibility of tissue engineering in the absence of a matrix, whereby sheets of cardiac stem cells are stacked on top of each other to form a tissue. However, while tissue engineering provides a way of introducing cardiomyocytes into the heart, it is still unable to induce neovascularization of this newly formed tissue. Additionally, problems such as synchronization of the newly formed tissue with the rest of the myocardium, as well as conductivity of the novel tissue, are still nagging issues that need to be addressed before considering this as a viable treatment for CHD [5].

Finally, the timing of stem cell use in CVD plays an important role in the outcome of the treatment. In HF/MI, clinical studies done comparing early (<3days) vs late (2-3 weeks) administration of stem cells post MI showed little difference between the two modalities [3]. In CHD, the windows to consider are in-utero *versus* post-natal administration of stem cells. The risk associated with in-utero administration of stem cells into a fetal heart remains quite high, and such a study currently would be too dangerous to perform. Animal models are being used to explore this alternative, and the potential for utilizing this method in treating CHD in humans warrants close follow up of these trials [7].

Though stem cells offer an incredible opportunity to treat conditions previously considered untreatable, the divide between research and clinical application is still vast. This is particularly the case when considering the use of stem cells in CHD. While stem cells are being touted as the next step in the treatment of HF and MI patients, very little progress has been made in the field of CHD, and understandably so. The complexity of embryonic heart formation is such that even after decades of extensive research, the scientific community still lacks an understanding of many processes involved in heart development. And if we can't understand how the embryo does it, it might be a little hasty to expect ourselves to do it. In the sea that is the embryonic heart, we are still learning how to swim.

That's not to say that stem cells cannot play a role in cutting edge research in the field of CHD. In fact, one can argue that there is no better system to model CHD today than in stem cells. Using cells from a patient with CHD to create cardyomyocytes gives us an unprecedented cellular view into the effect of a genome with CHD. Furthermore, creating cardyomyocytes from patients with CHD provides us with an outstanding system for drug discovery.

To claim that stem cells will soon have a role in the clinic of pediatric cardiologists may be wishful thinking. But they most definitely allow researchers to understand the pathology of CHD, and they provide an excellent venue to discover new treatments.

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