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Stem Cell Therapy: Healing or Hype? Why Stem Cell Delivery Doesn't Work

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Abstract

During the last two decades, there has been a surge in the development of stem cell therapies to treat numerous debilitating diseases. Cardiovascular disease is a leading target of this research due to the minimal proliferative and regenerative capabilities of the heart. These studies have quickly progressed to clinical trials; however, the initial enthusiasm has faded as outcomes from these studies have led to disappointing and inconsistent results.[1] This Viewpoint offers an explanation as to why stem cells have yet to demonstrate a significant benefit in patients suffering from cardiovascular disease and how these challenges should be addressed.

Subject Terms

Biomaterials; Stem Cells; Myocardial Regeneration; Myocardial Infarction

Cell Type Doesn't Seem to Matter

It is currently unknown which cell lineage provides the greatest potential in regenerative effects. While most cardiac clinical trials have delivered mesenchymal stem cells (MSCs) or bone-marrow derived stem cells (BMSCs), others have employed adipose-derived stem cells (ASCs) and cardiac stem cells (CSCs).[1,2] Yet, regardless of the cell type used, stem cell trials for cardiovascular diseases have not yielded clinically meaningful outcomes, though most have only been statistically powered to demonstrate feasibility and safety.

MSCs are advantageous because they can be delivered to patients without the need for immunosuppression, and secrete numerous anti-apoptotic and angiogenic growth factors.[3] In 2014, 30 patients were enrolled in a multicenter, double-blind trial and randomized to receive an intramyocardial injection of 25 million MSCs or cell medium concurrent with left ventricular assist device (LVAD) implantation. The authors concluded that administration of MSCs was feasible and safe with a trend towards functional efficacy.[3]

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None.

BMSCs are commonly administered in cardiac trials and are attractive due to their proven safety and paracrine effects.[4] A BMSC trial published in 2013, randomized 200 patients with acute myocardial infarction (MI) to an open-labeled, controlled trial with two BMSC groups. These cells were administered via intracoronary injection at one of two time points after acute MI, and end-point data was collected four months after injection. The authors determined that intracoronary infusion of BMSCs at either time point did not improve left ventricular (LV) function.[4]

ASCs offer a readily available autologous cell type that can easily be procured from the patient. The first randomized, placebo-controlled double-blind trial to assess safety and feasibility of ASCs to patients with ischemic cardiomyopathy was completed in 2014.[5] Perin *et al.* determined that isolation and transendocardial injection of autologous ASCs was safe, and their results suggested that the cells may preserve ventricular function and myocardial perfusion.

Finally, CSCs have demonstrated the ability to regenerate myocardial tissue in preclinical studies and can be isolated from the patient during surgical intervention. Chugh *et al.* reported the first in-human, phase 1, randomized, open-label trial of autologous c-kit+ CSCs in 33 patients with heart failure undergoing CABG.[6] At 12 months, the authors confirmed safety of CSC isolation and delivery, and observed a reduction in infarct size with an increase in viable tissue.

Although many trials have demonstrated safety of stem cell delivery, there have been many conflicting results in terms of actual therapeutic benefit. A 2014 study found over 600 discrepancies in 133 reports from 49 BMSC trials.[7] Notably, they found that only trials that had discrepancies reported a significant increase in LV function, whereas trials with minimal discrepancies showed no functional benefit of BMSCs. This report is not exhaustive of all cardiac stem cell trials; however, it raises major concerns about proper study design.

Cardiac clinical trials have been successful in demonstrating feasibility and safety of stem cell delivery to the heart, yet, have been unable to show significant functional benefit. Conversely, preclinical studies present promising therapeutic improvements. These studies have demonstrated that a *statistically* significant result does not necessarily translate into a *clinically* significant improvement. It is therefore crucial to determine the cause of the disappointing and inconsistent results seen in the clinic.

Method of Cell Delivery and Why It Matters

The main stem cell delivery methods in cardiac clinical trials have included intracoronary, intramyocardial, transendocardial, and transepicardial injection.[2,8] Intracoronary infusion is popular for BMSC transplantation[8], yet has serious limitations. This delivery method relies on successful homing of the cells to the damaged tissue and subsequent extravasation and retention. Furthermore, if the cells successfully navigate these obstacles and reach the damaged tissue, they are then subjected to a hostile microenvironment, leading to poor cell survival.[8]

Direct injection into the myocardium may be preferred, since the cells are deposited directly into the area of intended therapy and do not rely on successful homing. Yet, injection through a needle has its own shortcomings, and post-transplantation viability can be as low as 1–32%.[9] While part of this low transplantation viability can be attributed to a harsh host microenvironment, the first incidence of damage actually occurs during the injection process.[9–11] When cells are driven through a needle, they are subjected to mechanical shear forces and extensional stretching forces which can fatally damage their membranes.[9,11] Thus, before the cells even reach the host tissue, they are subjected to mechanical forces which lead to significant cell lysis. Once *in vivo*, the necrotic cells will merely have an acute inflammatory effect.

Given the functional improvements cited in preclinical models, it is likely that the low numbers of viable cells post-transplantation are still adequate to elicit a beneficial response. However, when translated to the clinic, it appears that post-transplantation viability plays a much larger role.

How to Protect Cells

Due to the shortcomings of stem cell delivery and the lack of a suitable microenvironment post-transplantation, there is a need for minimally invasive delivery modalities that protect cells during delivery and provide them with a matrix at the host delivery site.

Cardiac cell patches are biomaterial scaffolds generally composed of either biologically- or synthetically-derived materials which provide cells with a microenvironment suitable for survival and differentiation. The scaffolds prevent anoikis, a form of programmed cell death that occurs when cells lack proper extracellular matrix (ECM) or cellular attachments.[12] Due to the alterations in the ischemic myocardial ECM, viability of transplanted cells may be enhanced by prior seeding on a biomimetic scaffold.[12–13] For example, Kim *et al.* developed a nanopatterned cell patch that enhanced retention and viability of cardiosphere-derived cells when transplanted into a rat MI model, leading to preserved myocardial thickness.[14] The safety and feasibility of a collagen cardiac patch was investigated in the MAGNUM phase I clinical trial, in which one group of patients received an injection of autologous BMSCs while the other group received a collagen matrix seeded with the same number of BMSCs. The authors observed statistical differences between the two groups at 10-months post-treatment, in which LV end-diastolic volume was significantly reduced and infarct thickness increased in the matrix-treated group compared to the cell-only group.[15] These data indicate the possible clinical benefit of a cell-seeded matrix versus cells-only treatment strategy.

In 2013, Shudo *et al.* expanded on patch technology by developing a smooth muscle cell-endothelial progenitor cell bi-level cell sheet that significantly increased functional microvasculature and myocardial function in a rodent ischemic cardiomyopathy model.[16] This strategy circumvents the scaffold by using pericytes as supporting structures, and mimics the native orientation and interaction between these cells.

While there has been significant progress in the field of cardiac cell patches, widespread translation is yet to be realized due to the inability to create scaffolds of appropriate

thickness due to diffusion limitations and inadequate graft perfusion.[12] Additionally, implanting the patch requires an invasive procedure which may limit its clinical relevancy for the treatment of acute MI. Nonetheless, continued preclinical and clinical translation of biomaterial scaffolds are necessary to understand their full therapeutic potential.

Hydrogels are 3-dimensional water-swollen polymeric matrices that can mimic physical and biochemical properties of host tissue. Like cardiac patch matrices, hydrogels can be derived from both biologic and synthetic polymers.[10,12] Injectable hydrogels have been explored in efforts to combat both limitations of cell injection due to their biocompatibility and ability to undergo a rapid sol-gel transition *in situ.* Pre-encapsulation of cells within hydrogels can shield cells from mechanical forces and unfavorable distortions during injection. One suggested mechanism by which this occurs is that a layer of hydrogel near the needle wall undergoes shear-thinning behavior to flow as a fluid while the core of the hydrogel remains intact, protecting the cells and forming "plug flow".[9,11] This is a similar process to blood flow in small vessels where a cell-free plasma layer appears near the vessel wall and red blood cells flow along the central axis. The rapid self-healing properties of injectable hydrogels allows the gel state to reform *in vivo* and provide transplanted cells with a suitable environment to survive.[12] Cai *et al.* developed an engineered shear-thinning, injectable hydrogel and demonstrated that transplanting ASCs within the gel resulted in a 47% increase in cell viability compared to ASCs in saline at day 3 post-injection.[10] Furthermore, shear-thinning hydrogels have gelation properties permitting percutaneous catheter-based delivery to the myocardium. Thus, injectable hydrogels could significantly enhance the therapeutic benefit of transplanted stem cells, while maintaining the minimally-invasive nature of transendocardial catheter delivery.

Future Strategies

To fully harness the therapeutic potential of stem cell transplantation, we must uncover the mechanisms by which each cell lineage exerts their beneficial effect. Numerous stem cell lineages have been tested preclinically and have demonstrated a statistically significant functional benefit. Once in the clinic, however, the same functional benefit has yet to be achieved.[1] While, it is likely that some cells may be better candidates than others for myocardial regeneration, we are unable to determine the most effective cell type due to low transplantation viability and engraftment. Thus, we must determine the optimal transplantation vehicle that will protect cells during delivery and support engraftment into the myocardium thereafter. Various tissue-engineered constructs have demonstrated promise in preclinical models, and development of these materials is continuing to progress. Injectable hydrogels provide a unique opportunity to deliver the cells in a minimally-invasive manner, while protecting them from mechanical forces during the injection process and preventing anoikis *in vivo*. Regardless of the choice of biomaterial, all aim to provide the support that cells require when being transplanted. Thus, it is obvious that injecting a cell suspension will not induce a clinically significant response due to the massive cell death that occurs.

By optimizing the delivery vehicle, we will be able to elucidate the therapeutic mechanism of each cell type and thereby determine the most effective cell or combination of cells to

induce myocardial regeneration. Future studies should aim to determine the optimal composite of cells, biomaterial, and delivery method to successfully regenerate myocardial tissue and add to the arsenal of treatment strategies for cardiovascular diseases.

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