

Stem Cells in Cardiac Transplants: Pros & Cons

Vasiliki E Kalodimou

Director, Flow Cytometry-Research & Regenerative Medicine Department, IASO- Maternity& Research Hospital, Athens, Greece

Corresponding Author: Vasiliki E Kalodimou, Director, Flow Cytometry-Research & Regenerative Medicine Department, IASO- Maternity& Research Hospital, Athens, Greece, E-mail: kalodimou@yahoo.gr

Today in the United States, congestive heart failure afflicts 4.8 million people, with 400,000 new cases each year. One of the major contributors to the development of this condition is a heart attack which occurs in nearly 1.1 million Americans each year. It is easy to recognize that impairments of the heart and circulatory system represent a major cause of death and disability in the United States [1].

Heart attacks and congestive heart failure remain among the word most prominent health challenges. Recent research is providing promising results that adult and embryonic stem cells may be able to replace damaged heart muscle cells and establish new blood vessels. For those suffering from common, but deadly, heart diseases, stem cell biology and regenerative medicine represents a new medical frontier [2].

The destruction of heart muscle cells, known as cardiomyocytes, can be the result of hypertension, chronic insufficiency in the blood supply to the heart muscle caused by coronary artery disease, or a heart attack, the sudden closing of a blood vessel supplying oxygen to the heart. More than half of patients with congestive heart failure die within five years of initial diagnosis despite the advances in surgical procedures, drug therapy, and organ transplantation.

Researchers all over the world exploring ways to save lives by using replacement cells so that the weakened heart muscle can regain its pumping power [3]. The important types of cell that can be developed are the cardiomyocyte, vascular endothelial cell, and the smooth muscle cell.

The potential capability of both embryonic and adult stem cells to develop into these cells types is now being under investigation with the hypothesis being the restoration of heart function after heart attacks or congestive heart failure. This hypothesis has immense advantages over heart transplant, especially in light of the paucity of donor hearts available to meet current transplantation needs [4].

Recently, Orlic and colleagues reported an experimental application using hematopoietic stem cells for the regeneration of the tissues in the heart. His team found that mice which received the transplanted cells had greater survival rates than the mice with heart attacks that did not receive stem cells. They concluded that the hematopoietic stem cells responded to signals in the environment near the injured myocardium due to partial repair of the damaged heart muscle. They work reveal that the cells migrated to the damaged region of the ventricle, where they multiplied and became "specialized" cells that appeared to be cardiomyocytes [5].

Same, Jackson et al., reported that cardiac tissue can be regenerated in the mouse heart attack model after the infusion of adult stem cells from mouse bone marrow. Here the investigators purified a "side population" of hematopoietic stem cells from a genetically altered mouse strain. These cells were

then transplanted into the marrow of lethally irradiated mice. Similar to the study by Orlic et al., the analysis of the region surrounding the damaged tissue in surviving mice showed the presence of donor-derived cardiomyocytes and endothelial cells. The concluded that mouse hematopoietic stem cells may be delivered to the heart through bone marrow transplantation as well as through direct injection into the cardiac tissue, thus providing another promising therapeutic strategy for regenerating injured cardiac tissue [6].

Another study showed that human adult stem cells taken from the bone marrow are capable of giving rise to vascular endothelial cells when transplanted into rats. These stem cells demonstrate plasticity [7]. Like the mouse stem cells, human hematopoietic stem cells can be induced under the appropriate culture conditions to differentiate into numerous tissue types, including cardiac muscle. The hematopoietic cells could be identified on the basis of highly specific cell markers that differentiate from cardiomyocyte precursor cells, enabling the cells to be used alone or in conjunction with myocyte-regeneration strategies or pharmacological therapies [8].

Embryonic stem cells are another possible source population for cardiac-repair cells due to their ability to differentiate into any cell type in the adult body. This assumption was first described by Itskovitz-Eldor et al. who demonstrated that human embryonic stem cells can reproducibly differentiate into embryoid bodies in culture made up of cell types from the body's three embryonic germ layers. Among the various cell types noted were cells that had the physical appearance of cardiomyocytes, showed cellular markers consistent with heart cells, and demonstrated contractile activity similar to cardiomyocytes when observed under the microscope [9].

Kehat et al., keeping in mind the work by Itskovitz-Eldor et al., discover the structural and functional properties in early stage of cardiomyocytes in the cells from the embryoid bodies. The cells that have spontaneously contracting activity were positively identified by markers with antibodies to myosin heavy chain, alpha-actinin, desmin, antinatriuretic protein, and cardiac

troponin. The team have done genetic analysis of these cells and found that the transcription factor genes expressed are consistent with early stage cardiomyocytes. A next step in this research is to see whether the experimental evidence of improvement in outcome from heart attack in rodents can be reproduced using embryonic stem cells.

These discoveries in animal models present a new promising opportunity in the field of regenerative medicine by using stem cells to repair the damaged heart muscle. The results of the studies discussed here are evidence that adult stem cells may develop into more cell types. Hematopoietic stem cells appear to be able to develop not only into blood, but also into cardiac muscle and endothelial tissue. Because of their "plasticity" could be a viable candidate for heart repair.

Stem cell therapy and stem cell research have been a hot topic over the last several years, giving rise to much debate; but there are many pros and cons to stem cell therapy and research which must be taken under consideration before the medical community starts the potential therapies [10, 11].

The pros of stem cell research:

- Led to many therapies available to treat a range of diseases and disorders, from various types of cancer to spinal cord injuries.
- Stem cell research has shown that stem cells have an amazing ability to regenerate all areas of the body, repairing damaged or diseased tissues.
- It holds the key to reversing the effects of aging and prolonging our lives. Stem cell research has already found many treatments that help slow the aging process, and a pro to further stem cell research is a possible "cure" for aging altogether.
- There are no moral or ethical questions about the use of these types of stem cells (adult hematopoietic stem cells).

- Stem cells can only lead to progress and medical discoveries.
- The unique capacity of embryonic stem cells to replicate in culture and provide large numbers of replacement cells in tissue culture for transplantation purposes may give an advantage over the use of adult stem cells.
- Stem cells serve as the foundation of "cellular therapy".

The cons of stem cell research:

- Embryonic stem cell use and research rise ethical issues.
- It is unclear how adult stem cells could be used to generate sufficient heart muscle outside the body to meet patients' demand.
- Until now we don't know how long the replacement cells will continue to function.
- In the new replacement cardiomyocytes derived from stem cells we must know if they have the electrical-signal-conducting capabilities of native cardiac muscle cells.
- In the current animal models, the time between the injury of the heart and the application of stem cells affects the degree to which regeneration takes place, and this has real implications for the patient who is rushed unprepared to the emergency room in the wake of a heart attack.

In conclusion: stem cells have the remarkable potential to develop into many different cell types in the body. When the body is injured, stem cells "travel" to heal the damaged tissue, e.g. heart muscle. They do this by secreting local hormones to rescue damaged heart cells and occasionally turning into heart muscle cells themselves.

The initial research in the field used patient's own stem cells, derived from the bone marrow, because they were readily

available. Now researchers working in this area have moved on to evaluate more promising approaches, such as:

1. Highly selected stem cells from a donor around the time of a heart attack.
2. Patient's own cardiac stem cells late after a heart attack.
3. Highly selected, non-cardiac, stem cells from a donor later after a heart attack.

For the future the scientific community must answer a big variety of questions rise from research:

- ✓ Could the patient's cells be harvested and expanded for use in an efficient manner?
- ✓ Can a patient at risk donate their cells in advance, in order to minimizing the preparation needed for the cells administration?
- ✓ Can these stem cells be genetically "programmed" to migrate directly to the site of injury and to synthesize immediately the heart proteins necessary for the regeneration process?

Investigators are currently using stem cells from all sources to address these questions, thus providing a promising future for therapies repairing or replacing the damaged heart. However, the use of these cells in this setting is currently in its infancy and much remains to be learned about the mechanisms and the safety issues prior to their use.

Stem cell therapy for damaged hearts has yet to be proven fully safe and beneficial.

All stem cell studies have strict protocols, approved by the FDA for inclusion and exclusion criteria. (<https://clinicaltrials.gov/>).

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