The potential of treating cardiovascular disease (CVD) through stem cell therapy

By Raphaella S. Hull
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ABSTRACT

Cardiovascular disease (CVD) is a generic term that applies to diseases of the heart and blood vessels, with coronary heart disease being the number one cause of death for both males and females above the age of 65 in the United Kingdom (2009). Given the UK’s population structure, which has a large ageing society, and the increased prevalence of lifestyle induced risk factors such as type 2 diabetes, CVD is going to be a significant health problem throughout the 21st century. Cardiovascular diseases can deprive the cardiac muscle with oxygen which results in damage to the cardiomyocytes; this can consequently lead to numerous detrimental effects, which may eventually lead to heart failure. The regeneration of damaged heart muscle tissue through the use of stem cells has the potential to be a new and revolutionary method to treat heart failure.

INTRODUCTION

The field of stem cell research developed from findings by Canadian scientists Ernest A. McCulloch and James E. Till in the 1960s, when they published the first evidence of stem cell existence. It was discovered that stem cells are undifferentiated cells that have the remarkable ability to differentiate into specialised cell types, depending on their potency. In medicine, stem cells have the potential to repair damaged tissues as they are able to divide limitlessly to replenish these damaged cells, and have the ability to either remain stem cells or to become more specialised cells such as muscle cells or red blood corpuscles.

The two broad types of mammalian stem cells are embryonic stem cells, which are isolated from the inner mass of blastocysts, and adult stem cells, or somatic stem cells, which are found in adult tissues. Embryonic stem cells were first derived by James A. Thomson, an American developmental biologist, in 1998; he also derived human induced pluripotent stem cells in 2007. Pluripotent embryonic stem cells, found within human embryos, the foetus or umbilical cord blood, have the largest potential in medicine as, depending on when harvested, they are able to differentiate into almost any one of the 220 different cells in the human body. Most embryonic stem cells are derived from embryos that have been developed from female gamete cells in an in vitro fertilisation clinic, which are then donated for the purpose of research, with the consent of the donor. To grow the stem cells, they are removed from the blastocyst and cultured in a Petri dish in the laboratory. The stem cells divide and can then be divided into other dishes, eventually leading to large numbers of stem cells, which can be frozen and stored. (See Figure 1)
Adult stem cells are undifferentiated cells found in already developed tissues like the heart, kidneys and brain. They can also be found in the bone marrow, blood vessels, skeletal muscle and skin. They usually have the ability to develop into the cells of their resident organs in order to maintain and repair damaged tissue as well as maintaining the normal turnover of regenerative organs, such as blood, skin, or intestinal tissues. These stem cells may remain quiescent for long periods of time until they are required to maintain tissues, or replace tissue damaged by disease or injury. A common example of adult stem cells are hematopoietic stem cells, found in the bone marrow, which are able to differentiate into different types of blood cells. At first, adult stem cells were thought to have more limitations than the stem cells derived from embryos, and it was believed that adult stem cells could only give rise to the same type of tissue from which they originated. However, research suggests that somatic stem cells might have the capability to differentiate into other types of cells. A widely researched example of this is liver cells being able to produce insulin, which could be used to treat diabetics. This possible capability is known as plasticity or transdifferentiation and is under much investigation. A drawback of using adult stem cells is that the generation of large numbers of stem cells is difficult as there are a very small number of stem cells in each tissue and their capacity to divide is limited when they have been removed from the body. Scientists are investigating how to culture large quantities of stem cells and then manipulate them to generate specific cell types so they can be used to treat injuries or diseases.

There is a third type of stem cells which are known as induced pluripotent stem cells (iPSCs), which are a type of adult cells that have been genetically ‘reprogrammed’ to an embryonic stem cell-like state.

DISCUSSION

The potential use of stem cells is vast; possible treatments include regenerating bone using cells derived from bone marrow stroma, developing cells that are able to produce insulin, as mentioned above, to treat type 1 diabetes or repairing damage to the cardiomyocytes due to a particular CVD – the potential in treating CVD is the main focus of this research paper.

To treat diseases using stem cell therapy you would begin by setting up stem cell lines; a stem cell line is a family of cells that are constantly dividing and originate from a single group of stem cells. The group of cells has the following two traits:

- They can divide and create exact copies of themselves which is known as self-renewal
They have the ability to differentiate into the distinct precursors of any type of human cell. The precursor can then develop into a fully functional, specific cell type for example a hepatocyte or red blood corpuscle.

These embryonic stem cells lines are derived from blastocysts which at 7 days are made up of about 100 cells. In order to acquire the stem cell lines, cells are removed from the inner mass region of the blastocyst which have the ability to become any cell of the 210 different cells types in the human body. Once the cells are taken out they are cultured in a Petri dish containing nutrients and growth factors. When these cells divide a stem cell line is established which can be maintained indefinitely if kept at the right conditions. The growth factors are used to make the cells differentiate into more developed cell types.

Once a stem cell line is accomplished, specific genes must be activated in order to make the stem cells differentiate into any cell that is desired. If we could direct a stem cell to differentiate into a specific cell type then the possibilities for treatment would be vast; these cells would provide us with a renewable source of replacement cells and tissues that could be used to treat injuries and diseases. They also provide the possibility of drug-testing, allowing drugs to be tested directly on the cells they will affect. For example, you could test new drugs that have the potential to treat heart diseases directly on human heart cells that have been grown for this purpose. You would have to direct the stem cells you had removed from the blastocyst to differentiate into heart cells which would allow you to test the new drugs on those cells and the data would directly apply to humans. This would dramatically reduce the need for animal based research and could save vast amounts of time and money; it would not completely eliminate the need for animal based research as cell lines do not test the effects that drugs have on the whole body.

In addition to drug-testing, stem cells have the potential to be used to treat numerous human diseases and stem cell therapy could change the face of medicine and alleviate the suffering of many. However, stem cell treatments are not new. The first stem-cell-based therapy was in 1968, when the first successful bone marrow transplant was carried out; this therapy was used to treat a patient with leukaemia. Bone marrow is transplanted routinely to treat a variety of blood and bone marrow diseases, immune disorders and blood cancer. In the procedure mentioned, the patient’s existing bone marrow is destroyed and replaced by donor bone marrow; this is accomplished by injecting donor hematopoietic stem cells into the patient and
the bone marrow stem cells establish themselves in the patient’s bones. The
donated bone marrow cells can then change into the blood cells that the patient
requires which can treat the disease.

For those that suffer or are affected by the suffering caused by cardiovascular
disease then research into stem-cell-based therapies could prove revolutionary.
Stem cells could be used to replace heart cells that have been damaged, which
would thereby restore a patient’s cardiac function. The possible ways of treating
cardiovascular disease using stem cells includes the generation of new heart muscle;
stimulation of the growth of new blood vessels to repair damaged heart tissue;
secretion of growth factors, which are naturally occurring substances capable of
stimulating cellular growth proliferation and cellular differentiation.

Clinical trials have shown that treating CVD by stem-cell-based therapies is
possible and that it is an effective and safe way to treat both old and recent infarcts.
Adult stem cell therapy for treating CVD was available to the public in at least five
continents in 2007. A company with the name VesCell claims to offer a
‘revolutionary treatment for heart disease that actually rebuilds heart tissue using
the patient’s own stem cells.’ On their website it states that they were the first
company to successfully treat heart patients with stem cells.

The generation of new myocardial tissue could be achieved by, as mentioned
before, isolating stem cells which may then have the potential to be directed to
differentiate into heart cells; they could then be injected into a patient’s damaged
heart muscle where they could begin to grow and replace damaged tissues. After
much research it is now known that under the right conditions stem cells can be
stimulated to develop into new cardiomyocytes and vascular endothelial cells. The
cardiomyocytes are the cardiac muscle cells found in the walls and foundation of the
heart, which contract to expel the blood out of the ventricle thereby playing a key
role in maintaining the heart’s continuous rhythmical beat. The vascular endothelial
cells are those which form the inner lining of new blood vessels. The promising
ability of both embryonic and adult stem cells to develop into these specialised cell
types could be a way to restore heart function superseding cardiovascular disease.
This approach would have many advantages over difficult heart transplants,
particularly as the demand for donor organs far outstrips supply.

To test the potential of stem cells therapy to treat cardiovascular disease,
rodents such as mice and rats are often used as a model to study new therapies. The
rodents are bred genetically similar to the stem cells that they will be given; this
eliminates the problem of immune rejection, an issue in clinical trials which will be
addressed later. To begin testing the rodents, heart tissue has to be damaged in
order to create a model example of CVD. By placing a ligature around a major blood
vessel that supplies the heart, scientists are able to induce heart attacks, akin to a myocardial infarction, and thereby investigate treatments using stem cells. In one study, the experimental application of hematopoietic stem cells led to the formation of new cardiomyocytes in the mouse, as well as regenerated vascular endothelium and smooth muscle. It was presented that after nine days the myocardium that formed as a result of the injection of stem cells occupied 68% of the damaged portion of the ventricle - the transplanted bone marrow cells had replaced the dead myocardium with functioning cardiac tissues. It was also found that those who survived in greater numbers were the mice who had received the donor stem cells in comparison to those who had not. However, the long-term effects of the therapy after transplantation are still being researched. The afore-mentioned research implies that the hematopoietic stem cells were able to repair parts of the damaged region of the ventricle by differentiating into cells that appeared to be new cardiomyocytes, where they multiplied and replaced damaged heart muscle tissue. This research shows that it may be possible to have adult bone marrow cells differentiate into heart muscle cells.

A further study which made use of bone marrow cells demonstrated the regeneration of cardiac tissue though the introduction of adult stem cells from mouse bone marrow. Hematopoietic stem cells were transplanted into the marrow of lethally irradiated mice about 10 weeks before the recipient mice were subjected to induced myocardial infarctions. The heart attacks were brought about by the same method as before via tying of a major heart blood vessel. On analysis of the damaged heart muscle tissue it was shown that the hematopoietic stem cells had migrated to the area in response to signals in the injured heart and had subsequently differentiated into the types of tissue required for cardiac repair. The survival rate of the mice for this investigation was 26%. The study suggests that the bone marrow stem cells can be delivered to the heart both through bone marrow transplantation as well as injecting them directly into the damaged cardiac tissue. It has also been shown that hematopoietic human adult stem cells have the ability to produce vascular endothelial cells when transferred to rats. The stem cells demonstrated plasticity which meant they were able to form new blood vessels in the damaged area of the rats’ heart, which is a second potential way to treat CVD. Similar to the mouse stem cells, these cells, under the correct culture conditions, demonstrated the ability to be directed to differentiate into the numerous cardiac tissue types needed for repair.

Another exciting population of stem cells that could have the ability to repair damaged cardiac cells are embryonic stem cells. Embryonic stem cells are classed as pluripotent and are also capable of self-renewal. Embryonic stem cells have a large
capacity to replicate in culture, which would allow large number of replacement cells to be produced and used for transplantation purposes.

The studies mentioned show scientific breakthroughs in the stem cell therapy area and the rodent models present opportunities for treating CVD through the transplantation of stem cells, which would replace current methods of organ transplantation. The results of many studies that have been carried out have shown that adult stem cells may be able to differentiate into more cell types that previously thought, making their potential use for treating diseases far greater. In has been shown that hematopoietic stem cells not only have the ability to produce cells that develop into a variety of mature blood cells but that they can also develop into heart muscle and endothelial tissue.

However, in the studies mentioned the evidence to show exactly how stem cells improved heart function is controversial and the experiments need to scrutinised and evaluated in order to progress to actually being able to treat CVD using stem-cell-based therapies. There is also the risk that stem-cell based therapies could cause immune rejection in the recipient, which is a major obstacle to overcome before treatments can become widespread. Donated stem cells may cause a receiving patient’s immune system to see the new cells as foreign bodies and subsequently attempt to destroy them. One way to overcome this problem is to use the patient’s own adult stem cells, as this would eliminate the problem of rejection. A downside to this treatment is, however, that adult stem cells have a lower ‘plasticity’ that embryonic stem cells and are therefore harder to manipulate and direct in laboratories. It was thought that another solution to the problem of rejection would be to use induced pluripotent stem cells (iSPCs) but recently biologists at UC San Diego have discovered that these cells could also face ‘immune rejection problems’ if they were used in future stem-cell-based therapies. Also, iSPCs are only just being developed and subsequently too new to be used for transplantation as there is still research that needs to be done.

CONCLUSION

There is clearly a large potential for the use of stem cell therapies in the treatment of CVD. To achieve this, stem cells lines need to be accomplished and the cells then directed to differentiate into the cells required for transplantation. Embryonic stem cells have the widest potential as they can differentiate into any human cell, but this gives rise to the issue of immune rejection. If it were possible to direct adult stem cells to differentiate into the cardiac muscle cells required for muscle repair then these could be injected into the damaged area or into the recipient’s bone marrow where they could then work to replace damaged tissue.
This method far exceeds that of transplantation both in its efficiency and safety. There are practical aspects surrounding this method as to repair one damaged heart it would require a vast number of stem cells. There are also many questions that need to be answered before clinical stem cell therapies can take place. The longevity of the replacement cells in uncertain and replacement cardiomyocytes may not last long following therapy. Also, the replacement cells may not have the electrical-signal-conduction capabilities that the original cardiac muscle possessed so therefore the cardiac muscle would not function efficiently. In the future, if treating CVD using stem cell therapy becomes common practice it may be possible to harvest a person’s own stem cells and then store them in preparation for an episode of CVD. It may also be possible to create stem cells that are able to migrate to an area of injury when injected into a patient. With further research and trials, there is a promising future for stem-cell-based therapies which would enable us to treat and cure many countries’ major causes of death.

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