STEM CELL RESEARCH

TREATMENT AND PREVENTION OF CORONARY HEART DISEASE

BY

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Word count: Approx 2500

Grade awarded June 2006: PASS WITH MERIT

RESEARCH PAPER
BASED ON PATHOLOGY LECTURES AT MEDLINK 2005
ABSTRACT
Stem cells were first discovered in 1995, and have been the subject of continuous research ever since. Stem cells have been a very popular topic in the field of medicine for the last couple of years and can be related to every branch of medicine. They hold the promise of cures for those suffering from a wide range of diseases. By manipulating stem cells, cell-based therapies may develop into the most influential advancement of the 21st century. However there are moral and ethical issues to be considered. The leading cause of death worldwide is coronary heart disease. The basics of stem cells and their application in treating and preventing coronary heart disease will be discussed in the following article.

INTRODUCTION
The use of stem cells for treatment has been endorsed since haematopoietic cells from bone marrow were used in the treatment of cancer. The first human embryonic stem cell was isolated in 1998 by James Thomson at the University of Wisconsin-Madison. Since then, vigorous research on the discarded embryos has begun.

Stem cells are cells with a number of distinctive properties; they are able to proliferate for an unlimited number of times before they die, carrying out a process of self-renewal. They can give rise to specialized cell types through asymmetric cell division, producing one cell which retains its stemness, and the other cell which travels along a pathway to specialization. Stem cells offer the possibility of renewable sources of replacement cells and new tissues to treat many kinds of diseases, conditions and disabilities. There are three types of stem cells; embryonic stem cell, adult stem cell and cord blood stem cell.

Embryonic stem cells (ESCs) are pluripotent, meaning that they can grow into any cell type. They can be obtained from the undifferentiated inner cell mass of a blastocyst. The embryos used in these studies were created for the purposes of in-vitro fertilization (IVF) treatment. When they were no longer needed for that purpose, they were donated for research with the informed consent of the donor. Abnormal growth of these cells will form a carcinoma, a type of cancer. Many stem cell lines are produced using human embryonic stem cells. They are valuable to the scientists because experiments can be compared across both time and many laboratories.

Another way of getting embryonic stem cells is using the technique called Somatic Cell Nuclear Transfer (SCNT). SCNT can reverse the differentiation process, producing embryonic stem cells. It requires the extraction of a nucleus from a somatic cell to be put in an egg, the complex is triggered to develop as a viable foetus. The eggs need to reprogram the genome of the somatic cell, shutting off genes specific for the previous role of the somatic cell, and turning on genes needed for embryonic development. This process may cause damage to the genetic materials, which may produce genetically altered cells during mitosis. This procedure, called therapeutic cloning, raises ethical issues, as it involves the creation of embryos.
There is growing evidence suggesting that adult stem cells can differentiate into many different types of cells, contrary to what scientists originally thought. It involves transdifferentiation (stem cells switch into a cell type with characteristics of another tissue) and dedifferentiation (regression of a younger cell type along the pathway of differentiation). Plasticity is used to describe this ability that stem cells possess. This discovery challenged biological dogma stating that cell differentiation is in one direction only and progressively restrictive.

Current development of stem cell research shows that all types of stem cells are of use to medicine. They can be manipulated to produce cells that could be used to repair damaged lungs, they can be grown into different tissues and organs, such as prostate and muscles. Clinical trials have been performed, but are restricted to using the patient’s own stem cells.

Stem cell research is applied in the treatment of coronary heart disease (CHD), which is the leading cause of death in the world. CHD is caused by atherosclerosis, which is the accumulation of fat plaque, or cholesterol deposits in the blood. The function of the coronary artery is to provide nutrients and oxygen to the cardiac muscle to pump blood throughout the body. Insufficient oxygen supply to the cardiac muscle surrounding the coronary artery causes the destruction of cardiomyocytes, and in turns damage to the cardiac muscle during myocardial infarction. Angina may also occur when blood flow is not fast enough to meet the demand of the heart during exercise, or even walking for patient with CHD. This causes chest pain and discomfort. Over time, CHD causes heart failure, the heart cannot pump blood effectively to the rest of the body, leading to the deterioration of quality of life.

Coronary Heart Disease is the leading cause of mortality in developed countries and has a rising tendency in developing countries. It significantly contributes to morbidity and death rates in the middle-aged population. Nearly 30% of all disability cases are due to CHD. For CHD, non-modifiable risk factors are: age, heredity, gender and ethnicity. This is opposed to modifiable risk factors which are: high blood pressure, high cholesterol level, and use of tobacco, unhealthy diet and physical inactivity.

There is still no successful drug therapy for many acquired and congenital diseases, despite all the medical breakthroughs in the last century. This is also true for CHD. Treatments for heart diseases are: Advances in surgical procedures, mechanical assistance devices, drug therapy, organ transplantation, clot-busting medications and angioplasty. These treatments are reasonably effective for treating chest pain, reducing the risk of heart attack and improving heart function, but none has the ability to actually restore or repair damaged heart tissue. The aim of stem cell therapy is to repopulate the ailing heart muscle with cells that may help restore blood supply and help the heart regain its ability to contract more effectively and efficiently.
DISCUSSION
Due to the huge influence of cardiovascular diseases in the human population, clinical trials enrolled hundreds of subjects with end-stage heart disease. Stem cell research on heart diseases progress rapidly. Cell therapy could be used to treat people with failing organs such as creating a human heart using adult stem cells and replacing it with the damaged one without immune rejection. Repair must stand the test of time though, and longer studies need to be performed. In the future, bed-bound patients may even return to their normal lives.

One piece of research\(^1\) dated back to November 2003 suggests that patients’ own stem cells in their bone marrow can be used to treat themselves following a heart attack by improving their cardiac function and blood flow. This is achieved by the injection of granulocyte colony-stimulating factor, which boosts the stem cell level in the body by promoting stem cell production within the bone marrow. These supplemental stem cells help regenerate cardiac tissue and improve angiogenesis, forming new blood vessels. However, this is proven ineffective following the latest news\(^2\) in March 2006. But this will not discourage enthusiastic scientists from doing research on the effect of stem cells in heart diseases.

A study\(^3\) related to heart disease was performed on mice in 2001. Stem cells were isolated from the bone marrow of a mouse. A heart attack was induced in another mouse and stem cells extracted from the first mouse were injected into this second mouse. Results showed that stem cells began to multiply and transform into heart muscle cells, and migrate into 68% of the damage area of the heart. The adult stem cells also produced additional cells that formed new blood vessels. This is of great importance to the healing of heart tissue in patients who suffer from coronary heart disease.

For future treatment, haematopoietic stem cells are the best candidate for developing into cardiac tissues. These cells have the highest ability to switch cell lineage and become heart cells, offering a potential cure for heart disease. Adult stem cells extracted from the patients themselves can either be injected to their cardiac tissue or bone marrow. Stem cells injected into the bone marrow can respond to the signals of the injured heart, and then migrate to the area of damage. These stem cells can then differentiate into different types of heart cells which are needed for cardiac repair. However, introducing stem cells to the heart may cause damage to the heart, but through safety procedures, this problem can be overcome. Methods of introducing stem cells into body include administering a catheter into coronary heart arteries or the left ventricle myocardium or supply through a needle during a coronary artery bypass graft.

There are signals which trigger stem cell differentiation controlled by genes, chemicals secreted by other cells, physical contact with neighbouring cells and certain molecules in the microenvironment within the cell. If the conditions for stem cell development into cardiomyocytes can be elucidated through research, they can be implanted into patient’s heart tissues. Heart attack patients can then be revived using some new undamaged myogenic cardiac tissues.
In the future of preventive medicine, adult stem cells can be extracted in advance from people who have a high risk of coronary heart disease and cultured in-vitro to obtain enough for future use when they suffer from a heart attack. These cells can be stored in a stem cell bank and can be used immediately after the incident of a heart attack, shortening the time between heart attack and treatment. Regular health checks would have to be done on high-risk people. If there is decrease in functioning of the heart, which can be indicated by patients’ conditions and their electrocardiograms, then suitable amount of stem cells can be injected into the heart, to improve the function of their hearts. These people are highly advised to lead an active lifestyle by doing more exercise, stop smoking and not to consume alcohol excessively. This can be done through education for children and government promotion using the media. These are very important, as coronary heart disease is hugely influenced by environmental factors, which can be controlled by people themselves.

In the near future, adult stem cell therapy should develop at the fastest rate. This is due to various reasons. First of all, therapies relying on adult stem cells face fewer ethical challenges than those using embryonic stem cells. Next, to be effective therapeutically, stem cells must be made in sufficient quantity. Adult stem cells can now be produced to an infinite number using laboratory culture. Also, although it is harder to separate and purify adult stem cells which can be found all over the body, they can be located using protein markers on the surfaces of the cells. In addition, safety is a very important factor. Embryonic stem cells can develop into a teratoma if there is any error occurred during the growth, causing cancer. And finally, ESCs have significant problem of rejection, despite using histocompatibility antigens to select the best donor’s embryonic stem cells in allogenic transplant greatly reduces the severity of graft-versus-host disease, cancer-induced immunosuppressant drugs are still required for patients. Taking everything into account, embryonic stem cells can be seen as having a limited medical application.

Controversy has always surrounded stem cell research. The latest one is the controversy concerning the South Korean scientist Hwang Woo-suk. In November 2005, it was discovered that eggs used in his research were donated by his staff, in contravention of international guidelines. After less than a month, he was subjected to allegations regarding his fabricated results in one of his research papers. This news had a huge worldwide coverage, increasing the concern of everyone in society. It should be stressed that tighter peer review, diligence and high verification standards should be met, especially when performing research on a sensitive topic like stem cells.

Bioethics is the one of the main issues in stem cell research and embryonic stem cells feature strongly. The status of the early embryos has never been decided. Some people, mainly scientists who support stem cell research, believe that the early embryo is just a ball of cells and nothing more. The embryos do not have a
sufficiently developed nervous system to feel pain, so they should not be considered as alive. Other people, mainly religious people and anti-science politicians, think that from contraception onwards, an embryo has the full status of a human and embryos used in stem cell research are purely treated as a resource and no longer as a whole. Therefore, they believe ESC research should be banned.

Different countries also hold different views. Some countries are more open-minded than others when supporting scientific research, therefore providing more funding for stem cell research and allowing more types of research being carried out. There are bans on embryonic stem cell research in many nations. For United Kingdom, scientists are allowed to isolate stem cells from embryos left over from IVF, and to clone its stem cells for research purpose.

Relatives of patients may want the research to speed up so that cell therapy can be used in the near future, so that the patients can benefit from the application of stem cells before the patients die. Thousands of helpless patients have desperate medical needs and are currently waiting for help. Different people have their own different beliefs, a compromise needs to be reached where everyone is satisfied.

CONCLUSION
Although human stem cell research is still in its infancy, there are many questions that remain to be answered and hurdles ahead to be overcome, there is no doubt that stem cell research is making a rapid progress. A great deal of social and scientific research still exists, although lots of research is needed in order to make the world confident in stem cell research and to start clinical trials. Stem cells hold promise for regenerating new tissues and organs for the bodies. If the development of stem cells continues, and if regenerative medicine becomes a major treatment and therapy, everyone in the world can benefit from it and human life spans will increase.

There is still much more to learn about how stem cells work. A primary goal is to find out precisely how undifferentiated stem cells become differentiated. Also we need to know how to administer them safely and whether they will still work properly without any harmful effects over time. In the future, for patients with coronary heart disease, their cardiac tissues can be repaired using their own haematopoietic stem cells extracted from their bone marrow. High risk patients should have their stem cells from the bone marrow extracted and store them in stem cell bank for future uses.

It is unfortunate that the reality of stem cell biology is overshadowed by the hype in the media. The full potential use of stem cells to revolutionize the practice of medicine and improve the quality and length of life may still have a long way to go. Let us hope that stem cell research can overcome these struggles, help to change the face of human diseases and alleviate pain for the future generations.
REFERENCES
1. American Heart Association (2003), Growth factor grows stem cells that help heal hearts
   http://www.americanheart.org/presenter.jhtml?identifier=3016886
2. American Heart Association (2006), Getting adult stem cells on the move may not significantly repair heart
   http://www.americanheart.org/presenter.jhtml?identifier=3038289

OTHER REFERENCES
5. Deane-Drummond, C (2006), Genetics and Christian Ethics
   http://stemcells.nih.gov/info/basics/
10. National Institute of Health (2005), Can Stem Cells Repair a Damaged Heart?
11. Wikipedia, Stem cells
    http://en.wikipedia.org/wiki/Stem_cell
12. U.S. Food and Drug Administration (2004), Cellular Therapy: Potential Treatment for Heart Disease
    http://www.fda.gov/cber/genetherapy/celltherapyheart.htm
    http://www.globalchange.com/stemcells2.htm
14. Church of Scotland (2002), Embryonic and adult stem cells: ethical dilemmas
    http://www.srtp.org.uk/cloninf8.htm
15. Risk Factors and Coronary Heart Disease
    http://www.americanheart.org/presenter.jhtml?identifier=4726
16. BBC News (16th December 2005), S Korea cloning expert hits back
    http://news.bbc.co.uk/1/hi/world/asia-pacific/4533786.stm
17. Supercourse (2005), Epidemiology of Cardiovascular Disease
    http://www.pitt.edu/~super1/lecture/lec18821/