Embryonic
Stem Cell Research

BY

Helen Wong

Word count: Approx 2000

Grade awarded June 2006: PASS WITH MERIT

RESEARCH PAPER
BASED ON
PATHOLOGY LECTURES
AT MEDLINK 2005

ABSTRACT

This paper consists of a scientific basis for stem cell research and the future prospects of embryonic stem cells used in medical context. In the discussion section, we will look into the potential of using embryonic stem cells for treating AIDS. We will also discuss the ethical issues embryonic stem cell research raises.

INTRODUCTION

Stem cell research began in the 1960s by Canadian scientists Ernest A. McCulloch and James E. Till. Nowadays, research in therapeutic cloning is done by Dr. Ian Wilmut at the Roslin Institute near Edinburgh. Their aim is to create a stem cell line with motor neurone disease for drug testing.

Stem cells are unspecialized cells that have two important characteristics distinguishing them from other body cells. Firstly, as long as the host organism is alive, they can replenish their numbers for long periods. Secondly, they can differentiate in response to certain chemical signals, into specialized cell types. This ability allows them to act as a repair system for the body, replenishing other cells Medical researchers believe stem cell research has the potential to change the face of human disease by being used to repair specific tissues or to grow organs.

Stem cells are categorized both by their sources and their potency, their potential to develop into different cell types.

Types of Stem Cells

The potency of stem cells is divided into totipotent, pluripotent, multipotent and unipotent. Totipotent stem cells are found in a a clump of undifferentiated cells formed from the first few divisions of the fertilized egg cell. These cells can grow into any type of body cells. Pluripotent stem cells are the next generation derived from totipotent cells and are found in a blastocyst. They can grow also into any cell type. Multipotent stem cells can produce only cells of a closely related tissue cells. For example, haematopoietic cells evolve to form white blood cells, red blood cells and platelets; whereas stromal cells develop into bone, cartilage and other fibrous connective tissues. Unipotent cells are already differentiated, but retains the self-renewal property of stem cells.

At the moment, we obtain stem cells for medical and research purposes from adults tissues, embryoes or the umbilical cord.

Adult stem cells are undifferentiated somatic cells found in human tissues. They are mostly multipotent cells and have been used in treatments such as bone marrow transplants. Using adult stem cells from a patient own cell tissue eliminates any rejection by the immune system. However, adult stem cells are difficult to identify among mature tissues. They are also very rare and in most cases insufficient to repair damage to vital organs in adults. Culturing adult stem cells also presents a problem in the laboratory, since their potential to reproduce diminishes after about 10 times of replication, as their DNA sequence degenerates. It becomes difficult to expand their numbers in culture. Cord blood stem cells are derived from the blood of the placenta and umbilical cord after birth. They have been used to treat Gunther's disease, Hunter syndrome, Hurler syndrome and Acute lymphocytic leukemia since 1988. The treatment can be allogenic or autologous, depending on whether the stem cells come from the patient’s own cord blood or from a donor’s. However, cord blood cells have previously been limited to treating children. This is because the one of the greatest obstacles, said Ralph Vogler, MD, scientific program director

at the American Cancer Society, is getting enough stem cells from the cord blood to successfully treat an adult. Typically, cord blood contains only about 1/10 the number of useable cells that bone marrow does.

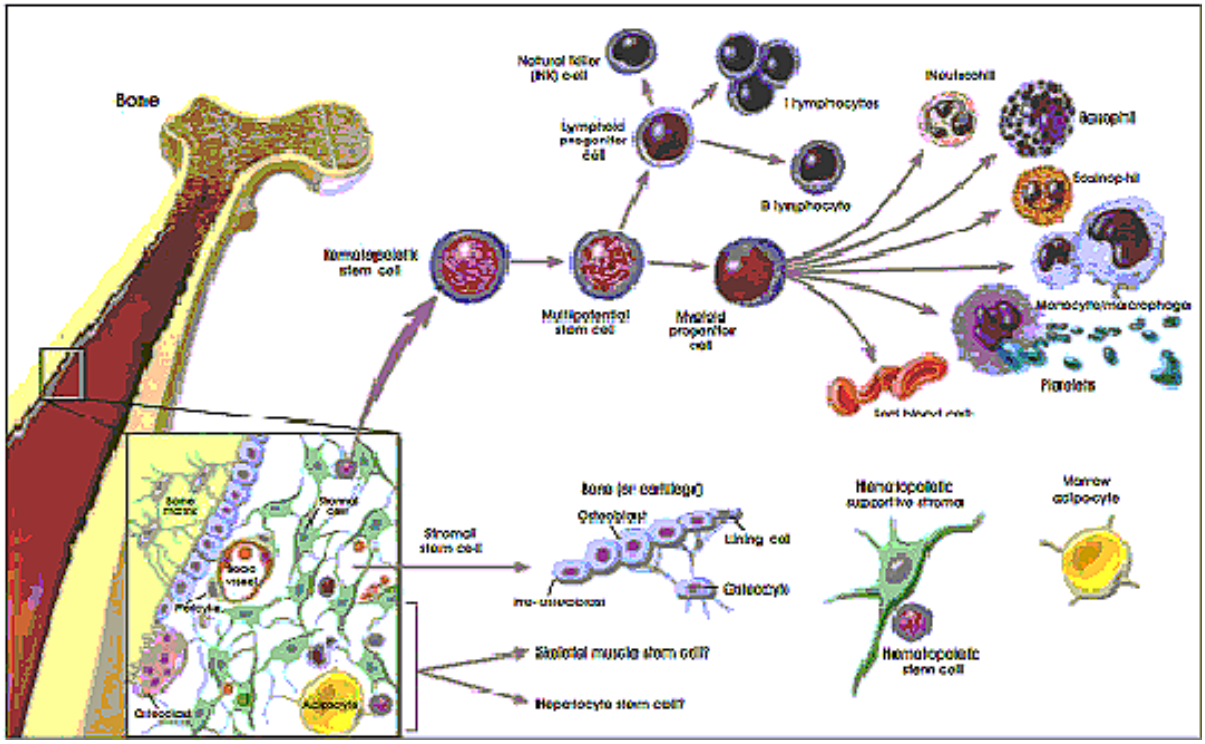


Figure 1. Hematopoietic and Stromal Stem Cell Differentiation

(© 2001 Terese Winslow, Lydia Kibiuk)

Embryonic stem cells are cultured cells obtained from a blastocyst, the thin-walled hollow structure in early embryonic development. The inner cell mass forms all the cells of the body, but are undifferentiated and therefore pluripotent. According to Dr. Michael Gross, such stem cells are extremely interesting for medical research because they have the potential to develop into any kind of body cell." Another significance of stem cells is that they can divide indefinitely to create a stem cell line for research purposes. Only embryonic stem cells, have the capacity to become any kind of human tissue and therefore the potential to repair vital organs. Embryonic stem cells hold great promise for treating degenerative diseases, including diabetes, Parkinson's, Alzheimer's, neural degeneration, and cardiomyopathies.

DISCUSSION

The Scientific Basis for Stem Cell Treatment

Embryonic stem cell (ESC) cultures are created by taking the inner cell mass from a blastocyst and putting it into a culture dish. These cells divide within a few days and are plated into several fresh culture dishes. This process is repeated many times, eventually yielding millions of ESCs. If, after six months, the cells keep dividing without differentiating, are still pluripotent, and are genetically normal, they are referred to as an ESC line.

ESCs are attractive to use in stem cell therapies because they are pluripotent and relatively easy to grow in large amounts. However, in reference to the Stem Cell Research Foundation, just injecting ESCs into a site of injury would probably result in a tumor growing in that spot. ESCs must first be directed to differentiate into the desired cells, such as heart muscle cells, blood cells, or nerve cells. To control ESC differentiation in cell cultures, scientists try different techniques, such as changing the chemical composition of the culture medium, altering the surface of the culture dish, or inserting specific genes into the cells.

At the moment, scientists are still working out the chemical signals needed to coax stem cells to grow into specific tissues. An example of research into signaling mechanisms is Dr. Daniel Besser’s work on Signaling Mechanisms in Embryonic Stem Cells, where he investigates signaling pathways and downstream targets genes, as well as the crosstalk of mouse embryo fibroblasts.

Cell Therapy

At the moment, cell therapy relies on replacing diseased or dysfunctional cells with healthy, functioning ones. They can be applied to treat cancer, Parkinson's and Lou Gehrig's Disease, spinal cord injuries and diabetes. A number of current treatments already exist, but most of them are not commonly used because they tend to be experimental and not very cost-effective.

Bone marrow transplants are an example of cell therapy in which the stem cells in a donor's marrow are used to replace the blood cells of the victims of leukemia and other cancers. Cell therapy is also being used in experiments to graft new skin cells to treat serious burn victims, and to grow new corneas for the sight-impaired. In all of these uses, the goal is for the healthy cells to become integrated into the body and begin to function like the patient's own cells. In a recent advance, pancreatic cells grown from stem cells were implanted into the body of a diabetic and began to produce insulin.

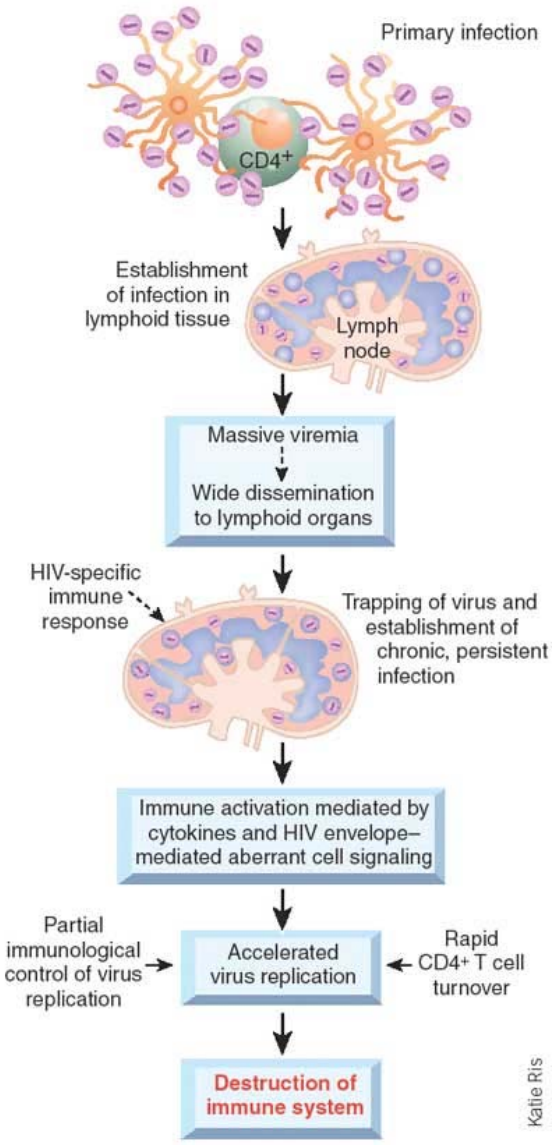
In the treatment for leukemia, patients often undergo radiation or chemotherapy to kill their cancerous white blood cells, destroying their immune systems at the same time. To restore their immune systems, these patients are given an infusion of bone marrow or umbilical cord blood, both of which contain stem cells capable of developing into every kind of blood cell.

Possibility of treating AIDS patients with stem cell therapy

To understand the prospect of such a treatment, we must first understand the causes of AIDS (Acquired Immune Deficiency Syndrome).

AIDS is caused by human immunodeficiency virus (HIV). HIV cannot penetrate broken skin, but is transmitted through the direct exchange of body fluids. As the virus enters the blood streams, macrophages and dendritic cells bind virus and shuttle it into the lymph nodes containing high concentrations of T Helper cells. The virus invades the T helper cells, establishing the infection.

Wide dissemination of the virus throughout the body's lymphoid tissues occurs. Since T helper cells are responsible for recognizing antigens and initiates the immune response of B and T cells, they multiply as the infection builds up. An immune response against the virus causes some protection, but a chronic persistent infection is established. The production of cytokines and cell divisions that regulate the immune response for protection also causes the replication of HIV inside cells. There is a rapid turnover of T helper cells ultimately leads to their destruction, and to a change in lymphoid tissues prevents immune responses.



In the past, HIV patients cannot be treated with stem cell therapy without a perfectly matched donor because the introduction of foreign white blood cells is most likely to cause a more severe immune response which will be fatal. However, with the possibility of therapeutic cloning, a genetically identical tissue can be created.

The idea comes from the use of stem cells in treating leukemia patients. All T lymphocytes (both helper and cytotoxic cells) leave the bone marrow and collect in the thymus to mature. Only mature lymphocytes carry out immune responses, but in HIV patients, the thymus has already been infected with HIV. All the matured T cells they produce are therefore infected.

With reference to Dr Jason Gill from the Monash University Medical School in Melbourne, Australia, whose team has identified and grown stem cells to regenerate a mouse's thymus, it has become a foreseeable possibility to regenerate a human thymus with stem cells. With therapeutic cloning, a perfect genetic match of the patient's thymus tissue can be produced and cultured. From this tissue, perfectly matched T cells can be produced and injected into the patient's blood to provide a temporary immune response for the body against other infections.

In future, it could also become possible to find a HIV resistant gene. Therapeutic cloning and gene technology can be combined, using the mitochondrial DNA of the stem cell as a vector to produce HIV resistant white blood cells. This, however, might raise ethical concerns over the genetic modulation of human beings.

CONCLUSION

While embryonic stem cells provide us with unlimited opportunities for research and medical advancement, there are still many key obstacles to overcome before stem cell treatments for AIDS patients can be implemented.

At the mean time, scientists are still looking for the correct medium for stem cell development. We are still unable to tell what coaxes hematopoietic cells into neurons, blood cells or walls of blood vessels.

Even if, and when, therapeutic cloning succeeds, the embryo produced will not be an accurate clone since the mitochondrial DNA cannot be removed along with the nucleus from the egg.

Currently, the creation of a stem cell line requires the destruction of a human embryo or therapeutic cloning, which is effective the creation of an embryo by removing the haploid DNA and the nuceus of an egg and replacing it with a diploid nuceus. Some believe is a slippery slope to reproductive cloning and equals the objectification of a potential human being. Representing the Catholic Church, Archbishop Tscherrig in Korea is quoted to have said ‘We do not oppose adult stem-cell research…’’ but ``We believe life starts at the moment of conception, and use of embryo is, to us, the killing of a human being, robbing a human being of his or her life…Life is the most basic human right.’’ On the other hand, a lot of the surplus human embryos available from IVF clinics have a high rate of genetic errors and would be unable to grow into a human being in any case. However, these are also unsuitable for ES cell research. Medical researchers argue that the use for embryonic cells, which will not develop into babies anyway without being injected into a womb, to treat existing people can be justified. Thus, a heated debate on when life begins starts.

This raises a problem for many governments to compromise between the need for medical research and the objections of religious groups. The United Nations has even recently passed a recommendation for member states to ban therapeutic and reproductive cloning. The UK government, however, have chosen to fund research on therapeutic cloning for medical purposes. To ensure the responsible use of stem cells, a stem cell bank has been created so that researchers can use cells from existing stem cell lines instead of creating their own.

REFERENCES

Salisbury, J. King's College School of Medicine and Dentistry (1997) Molecular Pathology, Taylor & Francis Ltd.

Gross, M. (2006) New cells for old. In Biological Sciences Review, Volume 18, No.3

Mary Jones (2000) Cambridge Advanced Sciences Biology, Cambridge University Press

Cancer, AIDS hope from stem cell study reported by Grant Holloway, CNN Sydney

http://archives.cnn.com/2002/WORLD/asiapcf/auspac/06/18/aust.stemcells/

Signaling Mechanisms in Embryonic Stem Cells reported by Dr. Daniel Besser (Helmholtz-Fellow)

http://www.mdc-berlin.de/englisch/research/research_areas/cancer/besser.htm

Cord Blood Transplants Help Adults with Leukemia, Option for Patients Without a Matched Bone Marrow Donor reported by American Cancer Society

http://www.cancer.org/docroot/NWS/content/NWS_1_1x_Cord_Blood_Transplants_Help_Adults_with_Leukemia.asp

Hematopoietic Stem Cells reported by National Institutes for Health

http://stemcells.nih.gov/info/scireport/chapter5.asp

Researchers Use Human Embryonic Stem Cells To Kill Cancer Cells reported by University of Minnesota

http://www.sciencedaily.com/releases/2005/10/051012084443.htm

Stem Cells and Potency from UC Davis Biotechnology Program

http://www.biotech.ucdavis.edu/Documents/Stem_Cell_Summary_Charts.pdf

Stem Cell Research Foundation

http://www.stemcellresearchfoundation.org

Immunology and HIV Additional Information about HIV Transmission by University of Arizona by William J. Grimes, Madeleine Lepointe, Jennifer Katcher, and Ken Williams

http://www.biology.arizona.edu/IMMUNOLOGY/tutorials/AIDS/HIVimmune.html