Stem Cells - A Review

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Abstract

Stem cell research has the potential to affect the lives of millions of people around the world. This research is now recently front page news because of the controversy surrounding the derivation of stem cells from human embryos. Realizing the promise of stem cells for yielding new medical therapies will require to grapple with more than just scientific uncertainties. The stem cell debate has lead scientists and non scientists alike to contemplate profound issues, such as who we are and what makes us human beings. The excitement and the controversy surrounding stem cells leads to lots of workshops conduction all over the world with representatives from various fields like molecular biology, immunology, cardiology, hematology, Neuro sciences, developmental biology, cancer, dentistry etc, all addressed the following scientific questions like what are stem cells. What are their sources? What biological differences exist between cells of different origin? What is the potential of stem cells for regenerative medicine and what obstacles must be overcome to make them useful for medical practices etc. On the other hand questions related to ethical issues, philosophy, law and other issues relevant to public policy consideration were considered. Hence an attempt has been made in this review to give a brief idea of the past, present and future of regenerative medicine.

Introduction

Research in Hematopoietic stem cells was done by Canadian scientists Ernest McCulloch and James E Till in 1960-1,2. The first use of bone marrow transplant was done by Schretzenmyr in 1937-3 from the stem cells of the bone marrow of adult.

Stem cells are unspecialized cells common to all multicellular organisms that can self renew indefinitely and differentiate into more mature cells with specialized functions. Stem cells that are able to differentiate into cell types beyond those of tissues in which they normally reside are said to exhibit plasticity. Stem cells are produced from the fusion of egg and sperm cell. The cells produced during the first few divisions are totipotent3 and can differentiate into embryonic and extra embryonic cell types.

Pleuripotent stem cells are descendants of totipotent cells and can differentiate into cells derived from the three germ layers. They arise from the inner cell mass and can become any type of tissue except the placenta. Multipotent cells can produce only cells of closely related family of cells like hematopoietic stem cells that can differentiate into RBC, WBC and platelets. Unipotent stem cells can produce only one cell type but have the property of self renewal.

Types of stem cells

Embryonic stem cells (ESCs): Human ESCs were successfully grown in the laboratory by Thompson et al, in 1998.4 These are derived from an early stage embryo. Fertilization of an ovum by a sperm results in the zygote. The zygote begins to divide 30 hours after fertilization and by third or fourth day the embryo is like a compact ball of 12 or more cells called Morula. 5-6 days after fertilization the Morula cells begin to specialize and form a hollow sphere of cells called Blastocyst. The outer layer of Blastocyst is called Trophoblast and the cluster of cells inside the sphere is called Inner cell mass. The cells of the inner cell mass are pleuripotent stem cells that give rise to cell types for ectoderm, mesoderm, and endoderm of the embryo. It is possible to remove these stem cells from the blastocyst and maintain them in an undifferentiated state in the Laboratory. The pleuriotpicity of ESCs is due to a gene that encodes a transcription factor SALL4, a protein that switches gene on and off. Other proteins include Oct 4 protein13 and Nanong protein 12 responsible for ESCs to remain undifferentiated. To be useful in medical therapy these ESCs will need to be differentiated into appropriate tissues for transplantation into patients. To be useful for medical therapies, cultured ESCs need to be differentiated into appropriate tissues for transplantation into patients. Researchers are beginning to learn how to achieve this differentiation.

Foetal Stem Cells (FSCs): These are primitive cells found in the fetus. Research with foetal tissue is limited to only to a few cell types. E.g. Neural stem cells used in rodent models with Parkinson’s disease, neural crest cells which can develop into nerves that innervate heart, gut, pigment cells, cartilage, bone and connective tissue. Hematopoietic cells found in foetal liver and blood, pancreatic islet progenitors.
Adult Stem Cell (ASCs): These are undifferentiated cells that occur in a differentiated tissue. Sources of ASCs include bone marrow, blood, eye, brain, skeletal muscle, dental pulp, skin, lining of the gastrointestinal tract, pancreas. These are multipotent. These Stem cells are located in sites called Niches. These Niches provide a specialized cellular environment needed for self renewal. Adult stem cells located outside the bone marrow are called Tissue stem cells. ASCs divide to replenish dying cells and regenerate damaged tissue. Regulation of differentiation in ASCs is by a protein Bmi-1, Notch pathway, sonic hedgehog and the Wnt developmental pathway. ASCs are difficult to identify and purify and when grown in culture are difficult to maintain in an undifferentiated state. Finding ways to culture ASCs outside the body is a high priority of Stem cell research.

Types of Adult stem cell Treatments:

Autologous Transplant: ASCs can be harvested and be used later to regenerate tissue by transplantation into same individual.

Allogenic Transplant: ASCs are taken from one adult and transplanted into another individual.

Stem Cell Markers:

Identifying a stem cell is not easy. Adult stem cells account for only one out of 10,000 cells. The situation with ESCs is little better since their source and identity are known without question. Scientists have developed a set of markers which simplify the identification of stem cells. These markers are divided into three groups;

1. Glycoprotein Receptors: present in the cell membrane. WBC carries CD4 and CD8 receptors specific for T lymphocytes. The proteins that bind to these receptors is called a Ligand and can be detected by a procedure called Immunofluorescence. Cells carrying CD4 and CD8 receptors are colored blue or green where as all other cells are colorless indicating that the cells are not differentiated. Fluorescent markers are often used in combination with fluorescence activated cell sorter (FACS) machine. A FACS machine can isolate a single stem cell from a population of more than 10,000 cells in one hour.

2. Cell Specific Gene Expression: some neurons are known to express a gene called Noggin which is not expressed by non neural tissue. Cells that express Noggin gene are detected by Fluorescent in situ hybridization (FISH). Cells expressing Noggin are colored blue. Stem cells that are not differentiated or are differentiating into non neural tissues are colorless.

3. Cell Specific Molecules: Beta cells are the only cells that produce insulin and make an excellent marker for differentiation of a stem cell into beta cells. All cells make a protein called Tubulin except neurons which make Neurotubulin which can serve as a marker for neural differentiation.

ESCs have special glycoproteins in their membrane like Stem cell antigen-1 and embryonic antigen-1

The presence of Telomerase is an indication that the cells are actively dividing as in Stem cells.

Clinical Application Of Stem Cells: Scientists were originally interested in stem cells because of the property of totipotency and plasticity. Many of the diseases described below can also be treated with Gene therapy, which attempts to correct the genetic abnormality by introducing a normal copy of the affected gene into the appropriate cells in the body. This therapy uses viral vector which sometimes can lead to deadly consequences. Stem cell therapy attempts to treat a disease by introducing human cells in the body which can restore normal health. Much of the work with stem cells is preclinics relying on the results obtained from mice or rats.

Leukemia:

Leukemia affects both lymphoid and myeloid cells. The standard treatment involves radiation and chemotherapy this can cause complete destruction of bone marrow leading to bone marrow suppression and necessitating transplantation. For many patients there simply are no suitable donors, in which case the outlook is grim. Stem cell therapy has the potential to treat all forms of leukemia with autologous transplants thus removing the need to find bone marrow donors. Stem cells isolated from the bone marrow of affected patients can be induced to differentiate into normal WBC and then grown in culture to increase their number. Once these cells are collected the patient's cancerous bone marrow is destroyed and replaced by stem cell derived blood cells.

Cancer:

Injection of human neural stem cells into intra cranial tumor of rodents produced cytosine de aminline an...
enzyme that converts a non-toxic prodrug into a chemotherapeutic agent. As a result, the injected substance was able to reduce tumor mass by 80 percent.

**Immune Deficiencies:**

A common form of immune deficiency is called severe combined immune deficiency (SCID). This disease destroys immune response and without special precautions, the patients die during the first year of life. One form of SCID linked to X chromosome a second form of SCID is due to mutation in the Adenosine deaminos gene, leading to toxic build-up of adenosine inside the cells, blocking normal maturation and activity. Conventional treatments involve bone marrow transplant. Gene therapy is used to treat ADA deficiency with moderate success. A combination of stem cell and gene therapy was established in 2002 by Dr. Alain Fischer. Of the eight patients treated, seven developed a functional immune system within three months.

**Diabetes:** Insulin controls the danger of high blood glucose levels but does not cure diabetes and sometimes long-term use may cause renal failure. In 2001 research teams in Israel and at the institutes of health in U.S. found a way to direct the differentiation of ESCs into beta pancreatic cells to secrete insulin. Other investigators are trying to repeat this accomplishment using ASCs. If this can be done, stem cells could be harvested from each Diabetic patient and differentiated into beta cells and then returned to the patient to cure the disease.

Liver Disease: Ornithine Transcarboxylase (OTC) is the enzyme secreted by the liver which converts ammonia to urea and excreted in urine. If OTC is defective, the blood levels of ammonia increase rapidly resulting in coma, brain damage, and death. HSCs can be isolated from the patient and stimulated to differentiate into liver cells and can be reintroduced into the patient. Once injected, tissue stem cells will colonize the liver and produce enough OTC to cure the disease.

**Cardiovascular Disease:** Coronary arteries carry blood to cardiomyocytes or heart muscle cells. If they become blocked or damaged, lack of oxygen to cardiomyocytes leads to massive heart attacks. Stem cells stimulated to differentiate into cardiomyocytes could be injected directly into the heart muscle in order to repair the damage. This is currently done in animal models.

**Neurological Diseases:** Alzheimer’s disease: Stem cells stimulated to differentiate into neurons and glial cells may be able to repair the damage to the brain caused by Alzheimer’s disease. It is still under trial in human beings.

**Parkinson’s disease:** Since the neurological damage caused by PD is restricted to one region preclinical research has shown that stem cell therapy may be successful in treating this disease.

**Spinal Cord Trauma:** Stem cell therapies attempting to repair a damaged spinal cord must provide neurons to reestablish the circuit and oligodendrocytes for insulation. Dr. Ronald McKay, a stem cell researcher has shown that mouse ESCs can repair some neural damage when injected into rats. But whether stem cells will be able to reestablish the circuitry and at the same time remyelinate the axons is yet to be determined.

**Drug Testing:** Human ESCs support basic research on the differentiation and function of human tissues and provide materials for testing that may improve the safety and efficacy of human drugs. Derived heart cells may be extremely valuable in identifying drugs before they are used in clinical trials, leading to safer and more effective clinical treatments.

**Barriers in Stem cell research in Regenerative medicine**

Use of Embryos for Stem cell research is controversial

New means to overcome the problem of tissue rejection must be found. Somatic cell nuclear transfer, genetic manipulation of stem cells. 10

Over time, stem cell lines may accumulate harmful genetic mutations. In addition, most stem cell lines have been cultured in the presence of nonhuman cells or serum that could lead to potential human health risks.

Researchers found that both ESCs and cancer cells express a protein called nucleostamin. Exact function of this nuclear protein is not known, but it appears to be a molecular switch that controls cell division. If cancer cells escape normal inhibitions of cell cycle by activating nucleostamin, this would imply that stem cells have a similar ability and should be handled with extreme caution. Hence additional studies will be needed to reveal more about the body’s own stem cells and their controls.
Conclusion

Although stem cell research is on the cutting edge of biological science, it is still in infancy. Studies of both ESCs and ASCs are required to most effectively advance the scientific and therapeutic potential of Regenerative medicine. In conjunction with research on stem cells, research on approaches that prevent immune rejection of stem cells should be pursued.

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