Stem cell therapy is emerging as a potentially revolutionary new way to treat disease and injury, with wide-ranging medical benefits. It aims to repair damaged and diseased body-parts with healthy new cells provided by stem cell transplants. Disease and disorders with no therapies or at best, partially effective ones, are the lure of the pursuit of stem cell research. Recently a plethora of work has been done in this field in world around including India. However, Stem cell research presents many ethical and scientific questions as well as future challenges. Nevertheless, stem cell therapy, a prologue to an era of medical discovery of cell-based therapies that will one day restore function to those whose lives are now challenged every day, is still at the beginning of the road.

Key words: Stem cell, adult stem cell, stem cell therapy.

Introduction

Stem cells are distinctive and versatile type of cells that can divide indefinitely and have a unique capacity to renew themselves and to give rise to specialized cell types. Although most cells of the body, such as heart cells or skin cells, are committed to conduct a specific function, a stem cell is uncommitted and remains uncommitted, until it receives a signal to develop into a specialized cell. Their proliferative capacity combined with the ability to become specialized makes stem cells unique.

Researchers have for years looked for ways to use stem cells to replace cells and tissues that are damaged or diseased. Recently, stem cells have received much attention.

In 1998, for the first time, investigators were able to isolate this class of pluripotent stem cell from early human embryos and grow them in culture.

In the few years since this discovery, evidence has emerged that these stem cells are, indeed, capable of becoming almost all of the specialized cells of the body and, thus, may have the potential to generate replacement cells for a broad array of tissues and organs, such as the heart, the pancreas and the nervous system.

Thus, this class of human stem cell holds the promise of being able to repair or replace cells or tissues that are damaged or destroyed by many of our most devastating diseases and disabilities.

What is Stem Cell?

A stem cell is a cell that has the ability to divide (self replicate) for indefinite periods—often throughout the life of the organism. Under the right conditions, or given the right signals, stem cells have the potential to develop into mature cells that have characteristic shapes and specialized functions, such as heart cells, skin cells, or nerve cells[1,2] [Figure 1].

Figure 1: Showing stem cell as a pluripotent cell

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Source of Stem Cells [Figure 2]
1) Embryonal stem cell
2) Adult stem cell

Embryonic Stem Cells
As their name suggests, they are derived from embryos (blastocyst) that develop from eggs that have been fertilized in vitro—in an in vitro fertilization clinic—and then donated for research purposes with informed consent of the donors.[3,4]

Growing embryonic stem cells in the laboratory.[5,6]
Growing cells in the laboratory is known as cell culture. Human embryonic stem cells are isolated by transferring the inner cell mass into a plastic laboratory culture dish that contains a nutrient broth known as culture medium. The cells divide and spread over the surface of the dish. [Figure 3]

Over the course of several days, the cells of the inner cell mass proliferate and begin to crowd the culture dish. When this occurs, they are removed gently and plated into several fresh culture dishes. Embryonic stem cells that have proliferated in cell culture for six or more months without differentiating, are pluripotent and appear genetically normal are referred to as embryonic stem cell line.

Adult Stem Cells
An adult stem cell is an undifferentiated cell found among differentiated cells in a tissue or organ, can renew itself and can differentiate to yield the major specialized cell types of the tissue or organ. The primary roles of adult stem cells in a living organism are to maintain and repair the tissue in which they are found.

Types of Adult Stem Cells[7,8]
In the 1960s, researchers discovered that the bone marrow contains at least two kinds of stem cells. One population, called hematopoietic stem cells, forms all the types of blood cells in the body. A second population, called bone marrow stromal cells, was discovered a few years later. Stromal cells are a mixed cell population that generates bone, cartilage, fat and fibrous connective tissue.

It was not until the 1990s that scientists agreed that the adult brain does contain stem cells that are able to generate the brain’s three major cell types—astrocytes and oligodendrocytes, which are non-neuronal cells and neurons, or nerve cells.

Sources of Hematopoietic Stem Cells
Bone Marrow
The classic source of hematopoietic stem cells (HSCs) is bone marrow. About 1 in every 100,000 cells in the marrow is a long-term, blood-forming stem cell; The marrow is aspirated by using a bone aspiration needle under local anaesthesia.

Peripheral Blood
As a source of HSCs for medical treatments, bone marrow retrieval directly from bone is quickly fading into history. For clinical transplantation of human HSCs, doctors now prefer to harvest donor cells from peripheral, circulating blood.
Researchers have found that they can coax the cells to migrate from marrow to blood in greater numbers by injecting the donor with a cytokine, such as granulocyte-colony stimulating factor (GCSF).

**Umbilical Cord Blood Stem Cells**

In the late 1980s and early 1990s, physicians began to recognize that blood from the human umbilical cord and placenta was a rich source of HSCs.

This tissue supports the developing fetus during pregnancy, is delivered along with the baby and, is usually discarded.

In recent years, however, the multipotent-stem-cell-rich blood found in the umbilical cord has proven useful in treating the same types of health problems as those treated using bone marrow stem cells and PBSCs.

Umbilical cord blood stem cell transplants are less prone to rejection than either bone marrow or peripheral blood stem cells. This is probably because the cells have not yet developed the features that can be recognized and attacked by the recipient’s immune system. Also, because umbilical cord blood lacks well-developed immune cells, there is less chance that the transplanted cells will attack the recipient’s body, a problem called graft versus host disease.

Both the versatility and availability of umbilical cord blood stem cells makes them a potent resource for transplant therapies.

**Potential uses of Human Stem Cells “Aladdin’s Lamp”**

Truly speaking stem cells are no less than “aladdin’s lamp” which promises to cure most of the diseases that plague the mankind today.

**Uses of Hematopoietic Stem Cells (HSCS): Present uses Leukemia and Lymphoma**[9,10]

Among the first clinical uses of HSCs were the treatment of leukemia and lymphoma, including Hodgkin’s disease, multiple myeloma and non-Hodgkin’s lymphoma. In these applications, the patient’s own cancerous hematopoietic cells were destroyed via radiation or chemotherapy, then replaced with a bone marrow transplant, or, as is done now, with a transplant of HSCs collected from the peripheral circulation of a matched donor.

**Inherited Blood Disorders**

Another use of allogeneic bone marrow transplants is in the treatment of hereditary blood disorders, such as different types of inherited anemia and inborn errors of metabolism.

The blood disorders include aplastic anemia, beta-thalassemia, Blackfan-Diamond syndrome, globoid cell leukodystrophy, sickle-cell anemia, severe combined immunodeficiency, X-linked lymphoproliferative syndrome and Wiskott-Aldrich syndrome.

Inborn errors of metabolism that are treated with bone marrow transplants include: Hunter’s syndrome, Hurler’s syndrome, Lesch Nyhan syndrome and osteopetrosis.

**Hematopoietic Stem Cells: Future Prospects**

**Hematopoietic Stem Cell Rescue in cancer Chemotherapy**[11]

Chemotherapy aimed at rapidly dividing cancer cells inevitably hits another target—rapidly dividing hematopoietic cells. Doctors may give cancer patients an autologous stem cell transplant to replace the cells destroyed by chemotherapy.

**Hematopoietic Stem Cell Therapy for Autoimmune Diseases**

The immune-mediated injury in autoimmune diseases can be organ-specific, such as type 1 diabetes which is the consequence of the destruction of the pancreatic beta islet cells. These autoimmune diseases are amenable to treatments involving the repair or replacement of damaged or destroyed cells or tissue.[12]

In contrast, non-organ-specific autoimmune diseases, such as lupus, are characterized by widespread injury due to immune reactions against many different organs and tissues.

The objective of hematopoietic stem cell therapy for lupus is to destroy the mature, long-lived and autoreactive immune cells and to generate a new, properly functioning immune system.[13]

Recent reports suggest that this replacement therapy may fundamentally alter the patient’s immune system. Hence stem cell therapy may hold a future promise to the treatment of autoimmune disorders.
Stem Cells and Diabetes

For decades, diabetes researchers have been searching for ways to replace the insulin-producing cells of the pancreas that are destroyed by a patient’s own immune system.\(^{(14)}\) Recently, hope for a permanent cure of diabetes has appeared, namely, the transplantation of islets isolated from donor pancreata into the livers of diabetic patients.

Some promising results have already been obtained with embryonic stem cells (ES cells) of both rodent and human origin.\(^{(15)}\) However, the potential use of ES cells for the treatment of diseases in humans is beclouded in controversy because of the ethical issues.

In theory, embryonic stem cells could be cultivated and coaxed into developing into the insulin-producing islet cells of the pancreas.

It is concluded that stem cells offer the greatest potential for the development of an abundant source of pancreatic islets, although specific obstacles must be overcome before this can become a reality.\(^{(16,17)}\)

Rebuilding the nervous system with stem cells

The past decade has seen impressive advances in the prevention and treatment of cerebrovascular disease. Several new therapies are under investigation to address the long-term disability of stroke survivors. Stem cell therapy offers exciting potential for ambitious cellular replacement to treat diseases such as Parkinson’s disease, Alzheimer’s disease or even replacement of the cell death that follows thromboembolic stroke. Longer-term safety and efficacy results should enhance our understanding of cell implantation therapy for the treatment of stroke.

Stem Cell Therapy for HIV\(^{(23)}\)

The hematopoietic stem cell has long been hypothesized to be a target of human immunodeficiency virus type-1 (HIV) infection that limits the potential for compensatory immune cell production.

Data have recently emerged documenting stem cell dysfunction in HIV disease and indicating that immune recovery from potent antiretroviral therapy is partly driven by new T-cell generation.

Effects of HIV on stem cell physiology, however, appear to be indirect, as stem cells are highly resistant to HIV infection. Despite the presence of surface receptors for HIV, the hematopoietic stem cell is not infectible with HIV and can serve as a resource for cellular therapies for AIDS.

Orthopaedics

It is now possible to repair articular cartilage using the patient’s own articular chondrocytes retrieved during arthroscopy and expanded \textit{in vitro}.

\textit{Pulmonary medicine}: cystic fibrosis, idiopathic pulmonary fibrosis, lung transplantation are the recent areas of pursuit.

\textit{Ophthalmology}: Stem cells hold promise to retinal
Stem cells: A new paradigm

degeneration, glaucoma and corneal disorders.

Pitfalls of Stem Cell Research

Stem cell research has been the centre of debate of recent times. Unfortunately, the medical application of stem cell technology is caught in a web of ethical dilemmas that is compounded by grave technical hurdles. There are several important issues which impinge on the future of stem cell research, which are not only of a scientific or technical nature, but are related to ethical and moral issues on the use of human embryonic or adult cells.

Ethical Dilemmas

To use an embryo as a source of body cells is a very different notion both scientifically and ethically. It treats the embryo purely functionally as a “ball of cells”, as a resource and no longer as a whole. The notion that it is okay to destroy embryos because they were created for research in the first place is wrong. This is PLAYING THE ROLE OF GOD!

Two Biological Hurdles to Stem Cell Therapy

Any stem cell therapy will have to clear two hurdles.

Immune Rejection

The first hurdle to clear is immune rejection. Patients receiving a graft of embryonic stem cells or adult stem cells sourced from unrelated donors would probably be treated in much the same way that organ transplant recipients are treated. The grafts would be matched to the individual patient and anti-rejection drugs would be used. If patients provide their own stem cells, then of course immune rejection is no problem. Leukaemia patients routinely rely on their own stem cells. After cancer therapy, which destroys stem cells, patients rely on the stored stem cells to rapidly restore their red and white blood cell counts to normal.

Long Term Sequelae and Neoplastic Potential

Any stem cell, adult or embryonic, has the ammunition it needs to give rise to cancer: an explosive ability to grow and to change into other types of cells. In fact, researchers now realize that at the heart of many common cancers lies an adult stem cell gone awry.

Any stem cell lines injected into patients have to be carefully tested first in animals to see if they give rise to cancer. Lymphoproliferative disease may occur during the first year, leukemia and myelodysplastic syndromes develop after several years, whereas solid tumors occur even later as long term sequelae.

Though cautious, researchers believe they will be able to tame the tendency of stem cells to form cancers.

Stem Cell- Indian Perspective

A lost science?

In Adi parva, one of the chapters of Mahabharata, it is said that Kauravas were created from pinda [a ball of flesh] which Gandhari delivered after two years of pregnancy. It was then handed over to the sage Dwapayan, which was then divided into one hundred parts and treated with herbs and ghee. The pieces were then covered with cloth and kept in a chamber to cool for two years; out of which the Kauravas were born.” There cannot be any other explanation for this….”

The ancient sages of India must have perfected the art of regenerating entire human beings from cells. In fact Mahabharata clearly describes the various stages of processing pieces of flesh, which is in fact closely comparable to modern techniques of harvesting and processing embryonic stem cells.[sans the sophistication!]. Perhaps stem cell research was altogether a lost science of ancient India.

The Rediscovery

By choice, chance or by coincidence, India too is into stem cell research. India has emerged as one of the major countries involved in Stem cell research. A country which succeeded in becoming an IT superpower is also trying to replicate its success in stem cell research. Apart from the pride and prestige earned by researchers in the country, the researches in stem cell technology are adding more horsepower to the booming economy of the country. Stem cell research in India made it to the headlines when the US department of health disclosed its interest in funding stem cell research in two Indian centres.

1) Reliance Life Sciences [RLS]

The Reliance life Sciences[RLS]; backed by the industry major Reliance Ltd ranks third among the top-10 institutes worldwide working on stem cells, as stated by NIH of the US and that too came just when the RLS was just 8months old! The center is headed by Dr Firuza
Parikh, the creator of the first ICSI [Intra Cytoplasmic Sperm Injection] child in India.

2) National Centre for Biological Sciences [NCBS]

The National center for biological sciences had been working on stem cells for quite long.[since 1999] and has three documented stem cell lines.

3) The Maulana Azad Medical College, Delhi is another major institution involved in stem cell research; and studies here are led by Dr Balakrishna Matapurkar, one of the pioneers of stem cell research in India.[27]

4) Another major institute involved in stem cell research in India is the L. V. Prasad Eye Institute, based at Hyderabad. The Institute caught the headlines recently when its doctors succeeded in transplanting a stem cell derived cornea to a patient who had lost his cornea- a treatment option available only in the US at that time.

The Indian Stem Cell Boom

Recently the Ruby Hall Medical Research Centre, a subsidiary of Pune-based Ruby Hall Clinic and Denmark-based biotechnology company Mesibo are soon to form a 49:51 joint venture with an aim to establish India’s largest cord blood storage facility at Pune. These measures got a pat on the back when NIH announced its interest in funding research in stem cells in the country. Recently contribution from the Indian researchers in the field of stem cell therapy have been recognized worldwide.[28,29]

Ethics: The Indian Perspective

When ethical jingoism dominated the scenario in the west, eastern countries like India and Singapore were taking rapid strides to reap the benefits of this science to the maximum possible extent.

Unlike the public opinion in the west, which is against researches in this field, the public opinion in many eastern countries including India is far more supportive. This may be partly due to the scientific temper inculcated by the epics and in numerous religious texts which are in fact acclaimed worldwide for their scientific value.

This openness is reflected in the Indian Department of Biotechnology [DBT]’s statement that India is open to stem Cell research; and it promptly made regulatory provisions to control unethical practices and in fact pioneered in bringing up a widely acceptable legal framework for research.

Indian Council of Medical Research

Guidelines for stem cell research/regulation in India (Oct. 2000)

Realising the potentials of this new technology in modern therapeutics and biomedical research it is strongly recommended that Stem cell research and its clinical applications should be promoted in the country.

The guidelines provides basis and recommendations for the stem cell research in India.

Take Home Message

Stem cells are distinctive and versatile type of cells.

Stem cells can divide indefinitely in culture and produce many types of new cells.

Pluripotent stem cells can produce most body cells.

Stem cell research provides the opportunity to advance our understanding of human biology and treatment of various diseases.

Stem cell research presents ethical and scientific questions as well as future challenges, Stem cell research is still at the beginning of the road.

References

Stem cells: A new paradigm

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Announcement

An International conference on “Emerging Trends in Haematology and Immunohaematology” is being organized to celebrate the Golden Jubilee of Institute of Immunohaematology from 31st January to 3rd February 2007 at Mumbai.

Further details will be available shortly at our website: www.iihicmr.org.