



Review Article

Stem Cell Therapeutics: A Review

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ABSTRACT

In the new millennium, where biology and biotechnology have replaced chemistry, researchers are exploring “biological solutions to biological problems”. Stem cells are the seeds of tissue repair and regeneration and a promising source for novel therapies. However, apart from hematopoietic stem cell (HSC) transplantation, essentially all other stem cell treatments remain experimental. Although the stem cell technology is just emerging, the regeneration of body parts is hardly a new concept. Stem cell therapy is a set of techniques that aim to replace cells damaged or destroyed by disease with healthy functioning ones. Stem cells are basic cells of all multicellular organisms having the ability to differentiate into wide range of adult cells. Modern therapeutics is having a lot of hope from stem cell research in the field of organ transplantation and replacement of lost tissue. It is the knowledge of regulators of stem cells at genomic and proteomic level which has opened the therapeutic usage of stem cells in the form of drug testing, neuron regeneration, treatment of bone defect, gene therapy and cell based therapy in the form of spinal cord injury, muscle damage, cancer therapy etc. Numerous challenges and technical barriers must be overcome before novel stem cell therapies can achieve meaningful clinical impact.

Keywords: stem cells, clinical applications, future perspectives

INTRODUCTION

The regenerative capability of a living creature was recorded as early as 330 BC, when Aristotle observed that a lizard could grow back the lost tip of its tail. Since then, there have been steady attempts at understanding the regenerative capabilities of human beings and we have seen an information explosion in the area of stem cell research in the last decade. Stem cells are unspecialized or undifferentiated cells having unique ability to proliferate indefinitely and can give rise to many different cell types. The ultimate goal of

stem cell therapy is to replace unhealthy cells with healthy ones allowing proper cell functioning in the human body.

This review sheds light on the origin of stem cells, their characteristics and regulation with enlightening comments on current research, potential clinical applications and future perspectives. It also focuses on the various challenges and barriers that we have to surmount before translating laboratory results to successful clinical applications.

Historical background

Stem cells have an interesting history that has been somewhat tainted with debate and controversy. In the mid 1800s it was discovered that cells were basically the building blocks of life and that some cells had the ability to produce other cells.

1908: The term "stem cell" was proposed for scientific use by the Russian histologist Alexander Maksimov at congress of hematologic society in Berlin.

1968: Bone marrow transplant between two siblings successfully treated severe combined immunodeficiency (SCID)

1978: Haematopoietic stem cells were discovered in human cord blood.

1981: Mouse embryonic stem cells were derived from the inner cell mass by scientists Martin Evans, Matthew Kaufman, and Gail R. Martin. Gail Martin is attributed for coining the term "Embryonic Stem Cell".^[1]

1995: Indian scientist Dr. B.G. Matapurkar pioneers in adult stem-cell research with clinical utilization of research in the body and neo-regeneration of tissues and organs in the body.^[2]

1997: Dr. B.G. Matapurkar's surgical technique on regeneration of tissues and organs was published. Regeneration of fallopian tube and uterus was published.^[3]

1998: James Thomson and coworkers derived the first human embryonic stem cell line at the University of Wisconsin–Madison.

1998: John Gearhart (Johns Hopkins University) extracted germ cells from fetal gonadal tissue (primordial germ cells) before developing pluripotent stem cell lines from the original extract.

2000s: Several reports of adult stem cell plasticity were published.

November 2007: Human induced pluripotent stem cells were generated from mature human fibroblasts. It is possible now to produce a stem cell from almost any other human cell instead of using embryos as

needed previously, albeit the risk of tumorigenesis due to c-myc and retroviral gene transfer remains to be determined.^[4]

11 October 2010: First trial of embryonic stem cells in humans.^[5]

2013: Scientists at Scotland's Heriot-Watt University developed a 3D printer that can produce clusters of living human embryonic stem cells, potentially allowing complete organs to be printed on demand in the future.^[6]

2014: Adult mouse cells reprogrammed to pluripotent stem cells using stimulus-triggered acquisition of pluripotency (STAP); a process which involved bathing blood cells in an acid bath (pH 5.7) for 30minutes at 37 °C. A little over a month after the publication of these findings, errors were discovered and the quality of the research has been widely questioned. Further irregularities regarding the mice used have emerged as recently as June 2014.^[7]

Characteristics and regulation of stem cells:

Stem cells are primal cells which are considered to be progenitor of more than 200 cell types present in adult body. The classical definition of a stem cell requires that it possesses two properties: Self renewal and potency. Self renewal means the ability to go through numerous cycles of cell division while maintaining the undifferentiated state. Potency means the capacity to differentiate into any mature cell type.

Potency definitions:

Potency specifies the differential potential of the stem cells.

Totipotent stem cells are produced from fusion of an egg and sperm cell. These cells can differentiate into embryonic and extra-embryonic cell types and can construct a complete organism.^[8]

Pluripotent stem cells are the descendants of totipotent stem cells and can differentiate

into cells derived from any of the three germ layers. These stem cells originate as inner cell mass within a blastocyst (Blastula).^[9] Multipotent stem cells can differentiate into a number of cell types, but only those of a closely related family of cells. Unipotent stem cells can produce only one cell type but have property of self renewal which distinguishes them from non-stem cells.

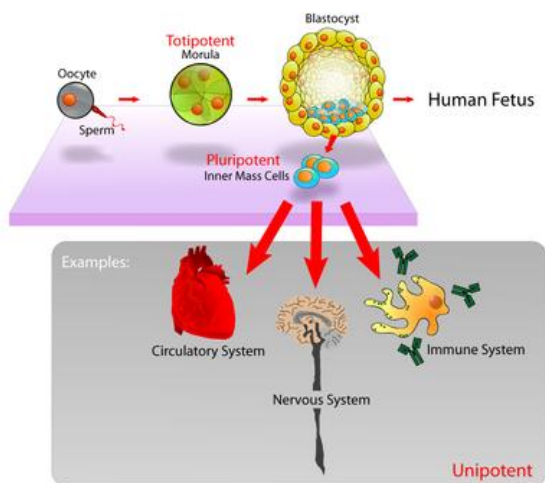


Figure 1: Potency of Stem cells.

Types of stem cells

Based on their origin, stem cells are broadly classified into two categories: embryonic stem cells and adult stem cells.

Embryonic stem (ES) cells are derived from the inner cell mass of blastocyst, an early-32 cell stage embryo. ES cells are pluripotent i.e. when given sufficient and necessary stimulation for a specific cell type, they can develop into each of the more than 200 cell types of the adult body except placenta. Nearly all research to date has made use of mouse embryonic stem cells or human embryonic stem cells. Both have the essential stem cell characteristics, yet they require very different environments in order to maintain an undifferentiated state.^[10,11]

Regulation of pluripotency of ES cells

Various transcription factors and proteins have been described which regulate the pluripotency of ES cells. The transcription factors Oct-4, Nanog and Sox 2 form the core regulatory network that ensures the suppression of genes that lead to differentiation and the maintenance of pluripotency.^[12]

These cells require specific signals to differentiate to the desired cell type; if injected directly, they will differentiate into many different types of cells, resulting in a teratoma. The directed differentiation of ES cells and avoidance of transplant rejection are just two of the hurdles that ES cell researchers still face.^[13]

Adult stem cells, also called somatic stem cells, are the undifferentiated cells found throughout the body that divide to replenish dying cells and regenerate damaged tissue.

Regulation of adult stem cells

Researchers have focused on uncovering the general molecular mechanisms that control self renewal and differentiation of adult stem cells.

- **Bmi-:** The transcriptional repressor Bmi-1 is one of the polycamb-group proteins which were discovered as a common oncogene activated in lymphoma and later shown to specially regulate haematopoietic stem cells.^[14]
- **Notch:** The role of Notch pathway has been demonstrated for several stem cell types including haematopoietic, neural and mammary stem cells.^[15]
- **Sonic hedgehog and Wnt:** These developmental pathways are also strongly implicated as stem cell regulators.

Bone marrow is a rich source of adult stem cells, which have been used in treating several conditions including spinal

cord injury, liver cirrhosis, chronic limb ischemia and end stage heart failure. The quantity of bone marrow stem cells declines with age and is greater in males than females during reproductive years.

Most adult stem cells are lineage-restricted (multipotent) and are generally referred to by their tissue origin (e.g. mesenchymal stem cell, adipose stem cell etc.). The use of adult stem cells in research and therapy is not as controversial as the use of embryonic stem cells, because the production of adult stem cells does not require the destruction of an embryo and the risk of rejection is also less in cases of an autograft transplantation. [16,17]

Bone marrow haematopoietic stem cells:

Haematopoietic stem cells are the precursors of all the blood cell types and can reconstitute the bone marrow after depletion caused by disease or irradiation. [18]

Neural stem cells (NSCs):

The existence of stem cells in the adult brain has been postulated following the discovery that the process of neurogenesis continues in adulthood in rats. NSCs may be sourced from the fetal, neonatal or adult brain. They self renew and differentiate to neurons, astrocytes and oligodendrocytes and are used in a variety of conditions. [19]

Adipose stem cells (ASCs):

These stem cells are plentiful, relatively easily accessed and are isolated by the method of liposuction. Autologous ASCs are being used for soft tissue engineering particularly for breast augmentation, fistulas in Crohn's disease and tissues damaged by radiation. In addition to soft tissue repair, ASCs are also in clinical trial for myocardial infarction and graft versus host disease. They have also been used in clinical trials for tracheo-mediastinal fistula, calvarial bone defect, skin ulcer and stress induced urinary incontinence. [20]

Amniotic stem cells:

Multipotent stem cells are also found in amniotic fluid, which are very active, expand extensively without feeders and are not tumorigenic. Amniotic stem cells are a topic of active research. Use of stem cells from amniotic fluid overcomes the ethical objections to using human embryos as a source of cells. [21]

Cord blood-derived multipotent stem cells (CB-SCs):

A certain kind of cord blood stem cell (CB-SC) is multipotent and displays embryonic and haematopoietic characteristics. Phenotypic characterization demonstrates the presence of embryonic cell markers and leukocyte common antigen CD45. CB-SCs display very low immunogenicity, which has therapeutic potential against autoimmune diseases like type 1 diabetes according to studies by Yong Zhao et al. [22]

Limbal stem cells:

Corneal epithelial stem cells are located at the basal layer of the limbus epithelium and provide for replacement of corneal epithelial cells that are damaged by disease. [23]

Endothelial stem cells:

These stem cells may be obtained from several sources e.g. bone marrow, umbilical cord blood and adipose tissue. They are effective in the stimulation of angiogenesis and in clinical studies requiring revascularization and remodelling of collaterals in atherosclerotic cardiovascular disease. [24]

Olfactory adult stem cells:

These cells have been successfully harvested from the human olfactory mucosa cells. [25]

Induced pluripotent stem cells (iPSCs):

These are not adult stem cells, rather adult cells are reprogrammed to give rise to pluripotent capabilities. iPSCs were first established in 2006 by Takahashi and Yamanaka using the retrovirus-mediated

transduction of four transcription factors (Oct3/4, Sox2, c-Myc and Klf4) into mouse fibroblasts. [26] Human iPSCs were established in 2007 by the transduction of either the same set of transcriptional factors or another set (Oct3/4, Sox2, Nanog, Lin28) into human fibroblasts. [5]

As a result of the success of these experiments, Ian Wilmut, who helped create the first cloned animal Dolly the sheep, has announced that he will abandon somatic cell nuclear transfer as an avenue of research. [27] Frozen blood samples can be used as a source of induced pluripotent stem cells, opening a new avenue for obtaining the valued cells. The discovery of iPSCs has opened up new avenues to generate patient- and disease- specific pluripotent stem cells. [28]

Current applications and future perspectives

Advances in stem cell research have explored many therapeutic avenues and the insight gained by a pilot proof of concept studies promise a plethora of unimaginable benefits.

➤ **Pharmacological and toxicological screening**

Human stem cells provide an important novel tool for generating in vitro pharmacological and toxicological test systems. In the development of new targeted therapies, as well as in critical safety issues, including hepato-, neuro- and cardiotoxicity, animal based tests are mostly unsatisfactory, whereas use of in vitro model systems is limited by the unavailability of relevant human tissues. Human embryonic stem cell lines may fill this gap which offer an unprecedented access to the human tissues. As a new opening in personalized medicine test systems, the generation of iPSC lines and their derivatives can provide patient- and disease- specific cellular assays for drug development and safety assessments. [29]

➤ **Gene therapy**

Human embryonic stem cells could be genetically manipulated to introduce the therapeutic gene. Recently published reports establish the feasibility of such an approach. Skin cells from an immunodeficient mouse were used to generate cellular therapy that partially restored functions in the mouse. This can also be used in treating human patients with immunodeficiency. [30]

➤ **Neurodegenerative diseases**

Research has been conducted to learn the role of neural stem cells in treating brain degeneration, such as in Parkinson's disease, Amyotrophic lateral sclerosis and Alzheimer's disease. Pharmacological activation of endogenous neural stem cells has been reported to induce neuroprotection and behavioural recovery in adult rat models of neurodegenerative diseases. [31]

➤ **Brain and spinal cord injury**

Stroke and traumatic brain injury lead to cell death, characterized by a loss of neurons and oligodendrocytes within the brain. Fetal NSCs are also being used for treatment of disabled ischemic stroke patients. The NSCs express several trophic and pro- angiogenic factors that promote revascularization that may be important in ischemic stroke. Since mesenchymal stem cells have been shown to differentiate into neurons in vitro, their ability to repair spinal cord damage has been tested in animal models. Autologous bone marrow stem cell transplantation in spinal cord injury patients has been documented to be safe and improve quality of life. [32,33]

➤ **Heart diseases**

Several clinical trials targeting heart diseases have shown that adult stem cell therapy is safe. However, none of these trials have proven efficacy. Stem cell therapy for treatment of myocardial infarction usually makes use of autologous bone marrow stem cells, however other types of adult stem cells such as adipose

stem cells may also be used. [34] The first successful integration of human embryonic stem cell derived cardiomyocytes in guinea pigs was reported in August 2012. The contraction strength was measured four weeks after the guinea pigs underwent stimulated heart attacks and cell treatment. The cells were found to contract synchronously with the existing cells. [35]

One of the most promising benefits of stem cell therapy is the potential for cardiac tissue regeneration to reverse the tissue loss underlying the development of heart failure after cardiac injury. Initially, the observed improvements were attributed to a transdifferentiation of BM-MSCs into cardiomyocyte-like cells. A more promising modern technique involves treating these cells to create cardiac progenitor cells before implantation to the injured area. [36]

➤ **Haematopoietic disorders**

In the past 40 years, haematopoietic stem cell transplantation (HSCT), also commonly referred to as bone marrow transplantation, has become the most successful of all cell therapies. In terms of treating blood disorders, HSCT has been used for immune deficiencies, leukaemia and lymphomas. HSCT is also routinely used to restore the blood system of patients undergoing aggressive doses of chemotherapy for blood and other cancers. HSCT can be autologous or allogenic. Autologous HSCT circumvents the problem of graft rejection. HSC therapies are in clinical trials for genetic diseases such as sickle cell disease and thalassemia. New developments in stem cell gene therapy offer a potentially safer therapy for sickle cell disease in the future. [37]

➤ **Baldness**

Stem cell therapy may lead to success in treating baldness. Researchers from the University of Pennsylvania and the New Jersey Institute of Technology have developed a technique to convert adult stem

cells into epithelial stem cells (EpSCs). By adding three genes to dermal fibroblasts, the scientists were able to convert them into iPSCs, which were then converted to EpSCs that are normally found at the bulge of hair follicles.

➤ **Tooth repair and regeneration**

Teeth exhibit limited repair in response to damage and dental pulp stem cells probably provide a source of cells to replace those damaged and to facilitate repair. The work on tooth regeneration has reached to a stage that it will be available to the general population in that decade.

➤ **Deafness**

Heller has reported success in regrowing the cochlear hair cells with the use of embryonic stem cells. [38]

➤ **Blindness and vision improvement**

Since 2003, researchers have successfully transplanted retinal stem cells into damaged eyes to restore vision. [39] The latest such development was in June 2005, when researchers at the Queen Victoria Hospital of Sussex, England were able to restore the sight of forty patients using the same technique.

In April 2005, doctors in the UK transplanted corneal stem cells from an organ donor. The cornea, which is the transparent window of the eye, is a particularly suitable site for transplants. In fact, the first successful human transplant was a cornea transplant. In 2009, researchers at the University of Pittsburgh Medical center demonstrated that stem cells collected from human corneas can restore transparency without provoking a rejection response in mice with corneal damage. [40]

Recently in January 2012, dramatic improvements in the vision of two patients of macular degeneration was reported after retinal injections of human embryonic stem cells. [41]

➤ **Diabetes type1**

In diabetes the insulin-producing beta cells are destroyed by the patient's own immune system. Transplantation of pancreatic beta Islet cells has been recently reviewed by Matsumoto. Xenotransplants of pig islets using encapsulation to address immune rejection is moving towards the clinic but concerns still exist for transmission of porcine endogenous retrovirus. The use of embryonic stem cell derived beta Islets in special subcutaneous capsules that induce minimal fibrosis may evolve into clinical trials shortly. [42,43]

➤ **Cancer**

Neural stem cells are entering clinical trials for targeting the destruction of inoperable glioblastoma. Researchers are genetically modifying the NSCs so they produce a prodrug activating enzyme that converts a non-toxic prodrug to a cytotoxic anticancer drug.

➤ **Bone regeneration**

Mesenchymal stem cells (MSCs) being the precursors of osteoblasts have been used for treating fractures. Genetic modifications of MSCs have also been employed to enhance their functionality. MSCs transduced with bone morphogenic protein2 (BMP2) and BMP4 have been shown to possess greater osteogenic potential. Centeno et al. have published MRI evidence of increased cartilage and meniscus volume in individual human subjects. [44,45]

➤ **Burn and skin injuries**

MSCs have been shown to undergo differentiation into keratinocytes in vitro and hence aid in regeneration of skin in cutaneous wounds. Deep burn wounds in rats undergo accelerated formation of blood vessels and granulation tissue and decreased inflammation following transplantation of MSCs. [46]

➤ **Infertility**

Culture of human embryonic stem cells in mitotically inactivated porcine

ovarian fibroblasts causes differentiation into germ cells. Human embryonic stem cells have been stimulated to form spermatozoa-like cells which could potentially treat azoospermia. Recently in 2012, oogonial stem cells, isolated from adult mouse and human ovaries were demonstrated to be capable of forming mature oocytes. [47,48]

Challenges of stem cell research

Stem cell research is a minefield of ethical problems because embryonic stem cells that offer the most potential for study must be harvested from human embryos. Adult stem cells offer a unique alternative in that they may be isolated and manipulated without harming the donor. However, several obstacles for use of adult stem cells exist. A major difficulty is to identify stem cells within an actual tissue culture and the in vitro systems for manipulating adult stem cell population are often not well defined.

Finally, there are additional issues even when cells are identified, isolated and grown. The new cells require implantation in a person and then they must essentially learn how to function effectively alongside a person's own tissues. A person's immune system may also trigger an immune reaction resulting in rejection of the new cells.

CONCLUSION

The potential of stem cell therapy to ease human suffering and dramatically affect disease has motivated scientists to research ways of enhancing current stem cell therapies and develop new ones. Stem cell therapy pose a bright future for the therapeutic world by promising treatment options for the diseases which are considered as non-curable now a days. While there are several barriers that need to be broken down before this novel therapy can be translated from laboratory to clinics, it is certain that the future is going to be exciting for all of us.

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