WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 5, Issue 01, XXX-XXX. Review Article ISSN 2277– 7105

STEM CELL RESEARCH: A LATEST APPROACH IN RECENT ADVANCEMENTS

Ghosh A, Dey M, Ganguly J, Shaw N, Parveen N, Mazumdar P, Mukherjee S*

Department of Pharmaceutical Technology, NSHM Knowledge Campus, Kolkata – Group of Institutions, 124, B.L Saha Road, Kolkata 700053, India.

Article Received on 30 Oct. 2015,

Revised on 22 Nov. 2015,
Accepted on 17 Dec. 2015,

***Correspondence for Author**
Mukherjee S
Department of Pharmaceutical Technology, NSHM Knowledge Campus, Kolkata – Group of Institutions, 124, B.L Saha Road, Kolkata 700053, India.
ghoshabhisek033@gmail.com
swarupananda.mukherjee@nshm.com

ABSTRACT

The present article is intended to discuss the importance of stem cells and their scientific research implications in treating disease with special emphasis to its future prospects. Stem cells are basic cells of all multicellular organisms having the potency to differentiate into wide range of adult cells. Self-renewal and totipotency are characteristic of stem cells. Though totipotency is shown by very early embryonic stem cells, the adult stem cells possess multipotency and differential plasticity that can be exploited for future generation of therapeutic options. Fortunately, the regulators of pleuripotency such as oct-4 & nanong protein are discovered and possibility of in vitro regulation of pleuripotency of stem cells is gaining strength. Genetic regulation of adult stem cells in the form of Bmi-1, Notch, sonic hedgehog & wnt gene is also being worked upon and future can be regulation of stem cell differentiation in vitro, in vivo or both. It is the knowledge of regulators of stem cells which has opened the therapeutic usage of stem cells in the form of neuron regeneration, treatment of bone defect, drug testing, gene therapy and cell based therapy in the form of muscle damage, spinal cord injury, cancer therapy etc. Cell based therapies might become commercial in coming years.

KEYWORDS: Stem Cell, Review, Clinical usage, Future prospects.

INTRODUCTION

Stem cells are primal cells common to all multicellular organisms that retain the ability to renew themselves through cell division and can be differentiated into a wide range of specialized cell types. Modern therapeutics is having a lot of hope from stem cell research in the field of organ transplantation and replacement of lost tissue. By virtue of self renewal and potency, stem cells can form various types of tissue cells. The regulators of stem cell growth at genomic and proteomic level are identified and we might be able to control stem cell in vitro. In developed countries, stem cell transplant has become a therapeutic option but in developing countries, it is still under trial phase. Ernest A. McCulloch and James E. Till in 1960s demonstrated the existence of stem cell.[1, 2] The embryonic (isolated from inner cell mass of blastocysts) and adult stem cells (found in adult tissues) are the two broad types of mammalian stem cells. In a developing embryo, stem cells can differentiate into all of the specialized embryonic tissues. In adult organisms, stem cells and progenitor cells act as a repair system for the body, replenishing specialized cells, but also maintain the normal turnover of regenerative organs, such as blood, skin or intestinal tissues. Stem cells can now be grown and transformed into specialized cells with characteristics consistent with cells of various tissues such as muscles or nerves through cell culture. Highly plastic adult stem cells from a variety of sources, including umbilical cord blood and bone marrow, are routinely used in medical therapies. Embryonic cell lines and autologous embryonic stem cells generated through therapeutic cloning have also been proposed as promising candidates for future therapies. [3] The Pubmed search till the date indicates the trend in stem cell research in Fig 1. This article focuses on types of stem cells, properties of stem cells, stem cell regulation with enlightening comments on clinical application and future aspects.

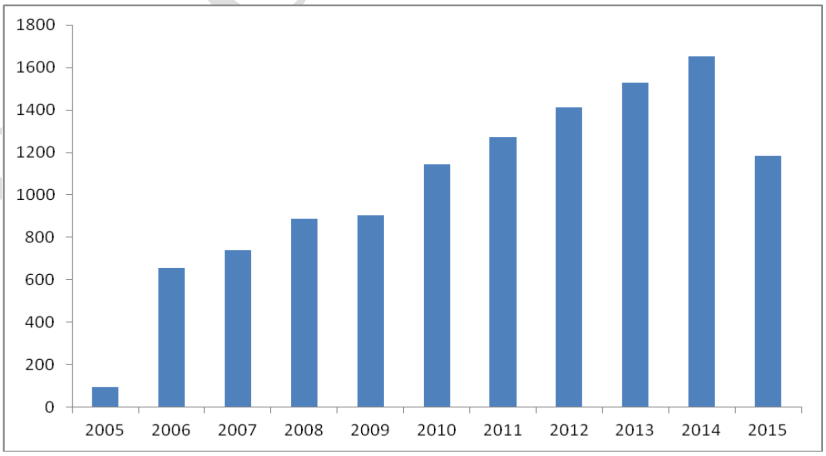

Fig 1: Trend in Stem Cell Research through Pubmed analysis

Properties of stem cell

Self-renewal and potency are the two basic classical properties. Self-renewal is the ability to go through numerous cycles of cell division while maintaining the undifferentiated state, whereas, potency is the capacity to differentiate into specialized cell types. In the strictest sense, this requires stem cells to be either totipotent or pluripotent - to be able to give rise to any mature cell type, although multipotent or unipotent progenitor cells are sometimes referred to as stem cells. Potency specifies the differentiation potential (the potential to differentiate into different cell types) of the stem cell.[6]

- Totipotent stem cells can differentiate into embryonic and extraembryonic cell types. Such cells can construct a complete, viable, organism.[6] These cells are produced from the fusion of an egg and sperm cell. Cells produced by the first few divisions of the fertilized egg are also totipotent.
- Pluripotent stem cells are the descendants of totipotent cells and can differentiate into nearly all cells,[6] i.e. cells derived from any of the three germ layers.[6]
- Multipotent stem cells can differentiate into a number of cells, but only those of a closely related family of cells.[6]
- Oligopotent stem cells can differentiate into only a few cells, such as lymphoid or myeloid stem cells.[6]
- Unipotent cells can produce only one cell type, their own,[6] but have the property of self-renewal that distinguishes them from non-stem cells (e.g. muscle stem cells).

Controversies In Stem Cell Research

Stem cell research is a minefield of ethical problems because stem cells that offer the most potential for study must be harvested from human embryos that are a few days old. In 1996, the birth of Dolly the sheep -- the world's first successfully cloned mammal -- ignited a firestorm of protest and concern. The most famous controversy in stem cell research has been Hwang's claim of cloning a dog. Hwang's work was able to offer an alternative to use of actual human embryo by cloning several human embryos, helping to eliminate the need for new embryos. Hwang claimed he had successfully cloned 30 human embryos, claims that have now been shown to be lies. Unfortunately, the use and study of embryonic stem cells are currently clouded by ethical controversy.

Biological uses of Stem cells

The stem cells are important for living organisms for many reasons. In the 3- to 5-day-old embryo, called a blastocyst, the inner cells give rise to the entire body of the organism, including all of the many specialized cell types and organs such as the heart, lung, skin, sperm, eggs and other tissues. In some adult tissues, such as bone marrow, muscle, and brain, discrete populations of adult stem cells generate replacements for cells that are lost through normal wear and tear, injury, or disease. Given their unique regenerative abilities, stem cells offer new potentials for treating diseases such as diabetes and heart disease. However, much work remains to be done in the laboratory and the clinic to understand how to use these cells for cell-based therapies to treat disease, which is also referred to as regenerative or reparative medicine. Laboratory studies of stem cells enable scientists to learn about the cells' essential properties and what makes them different from specialized cell types. Scientists are already using stem cells in the laboratory to screen new drugs and to develop model systems to study normal growth and identify the causes of birth defects. Research on stem cells continues to advance knowledge about how an organism develops from a single cell and how healthy cells replace damaged cells in adult organisms. Stem cell research is one of the most fascinating areas of contemporary biology, but, as with many expanding fields of scientific inquiry, research on stem cells raises scientific questions as rapidly as it generates new discoveries.

Present Scenario in Stem Cell Therapy

Following types of stem cell therapy is possible in present scenario:

- Allogenic stem cell therapy: matched or unmatched
- Syngenic stem cell transplant: Identical twin
- Autologous stem cell transplant
- Cord blood stem cell transplant
- Nonmyeloablative stem cell transplant

However stem cell therapy has some inherent complications such as infection, regimen toxicity, carcinogenicity, immune deficiency and mortality due to co-occurrence of complications. These factors make the usage of stem cell limited. These factors not only alarm the treating team but also open new areas of research.

Clinical Application and Potential Use of Embryonic and Adult Stem Cells

There are many ways in which human stem cells can be used in basic research and in clinical research. [11] These are.

1. Embryonic stem cells have been used to study the specific signals and differentiation steps required for the development of many tissues.
2. Genetic therapy: Embryonic stem cells benefit the gene therapy by the following ways:

- First human embryonic stem cells could be genetically manipulated to introduce the therapeutic gene. This gene may either be active or awaiting later activation, once the modified embryonic stem cells has differentiated into the desired cell type. Recently published reports establish the feasibility of such an approach. [12] Skin cells from an immunodeficient mouse were used to generate cellular therapy that partially restored function in the mouse. This can also be used in treating human patient with immune-deficiency.
- Embryonic stem cells may additionally be indirectly beneficial for cellular gene therapy. Since these cells can be differentiated into many cell types, including presumably tissue specific stem cells, they may provide a constant in vitro source of cellular material. Such "adult" stem cells derived form embryonic stem cells may thus be utilized to optimize protocols for propagation and genetic manipulation technique. [13]

3. Drug Testing: Because embryonic stem cells can proliferate without limit and can contribute to any cell type, human embryonic stem cells offer an unprecedented access to tissue from the human body. They will 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 [14,15] for example, new drugs are not generally tested on human heart cells because no human heart cell lines exist. Instead researchers rely on animal models. Because of important species-specific differences between animal and human heart, however, drugs that are toxic to the human heart have occasionally entered clinical trials, sometimes resulting in death. Human ES cells – derived heart cells may be extremely valuable in identifying such drugs before they are used in clinical trials, there by accelerating the drug discovery process and leading to safer and more effective treatments. [16-18]
4. Cell based therapies: It is perhaps the most important potential application of human stem cells. They generate cells and tissues that could be used for cells based therapies. Stem cells, directed to differentiate into specific cell types, offer the possibility of a renewable source of replacement cells and tissues to treat various disease.
5. Brain Damage8 [19,20]: In the case of brain injury although reparative process appears to initiate, substantial recovery is rarely observed in adults suggesting a lack of robustness. Recently from research conducted in rats subjected to stroke suggested that administration of drugs to increase the stem cell division rate and direct the survival and differentiation of newly formed cells could be successful.

6. Cancer: Researcher at Harvard Medical School caused intracranial tumor in rodents. Then they injected human neural stem cells. Within days the cells had migrated into the cancerous and produced cytosine deaminase, an enzyme that convents a non-toxic prodrug into a chemotherapeutic agent. As a result, the injected substance was able to reduce tumor mass by 80 percent. [21]
7. Spinal cord injury: Recently extensive study work is carried out in treating spinal cord injury. Scientist have treated the patient of spinal cord injury by isolating adult stem cells from umbilical cord blood and then injected them into damaged part of the spinal cord. [22]
8. Muscle damage: Adult stem cells are also apparently able to repair muscle damaged after heart attacks. Heart attacks are due to coronary artery being blocked, staring tissue of oxygen and nutrients. Days after the attack is over, the cells try to remodel themselves in order to become able to pump harder. However, because of the decreased blood flow this attempt is futile and results in even more muscle cells dying. Researchers found that injecting bone marrow stem cells, a form of adult stem cells, into mice, which had heart attacks, induced resulted in an improvement of 33% in the functioning of heart. The damaged tissue had regrown by 68%. [23]
9. Heart damage: Several clinical trials targeting heart disease have shown that adult stem cell therapy is safe. However none of these trials have proven efficacy. Recently the use of patients own bone marrow derived stem cells and peripheral blood derived stem cells is becoming popular. [17,18]

Recent Advancements.

Stem cells can be used to study development

Stem cells may help us understand how a complex organism develops from a fertilized egg. In the laboratory, scientists can follow stem cells as they divide and become increasingly specialized, making skin, bone, brain, and other cell types. Identifying the signals and mechanisms that determine whether a stem cell chooses to carry on replicating itself or differentiate into a specialized cell type, and into which cell type, will help us understand what controls normal development.

Some of the most serious medical conditions, such as cancer and birth defects, are due to abnormal cell division and differentiation. A better understanding of the genetic and molecular controls of these processes may yield information about how such diseases arise and suggest new strategies for therapy. This is an important goal of stem cell research.

Stem cells have the ability to replace damaged cells and treat disease

This property is already used in the treatment of extensive burns, and to restore the blood system in patients with leukemia and other blood disorders.

Stem cells may also hold the key to replacing cells lost in many other devastating diseases for which there are currently no sustainable cures. Today, donated tissues and organs are often used to replace damaged tissue, but the need for transplantable tissues and organs far outweighs the available supply. Stem cells, if they can be directed to differentiate into specific cell types, offer the possibility of a renewable source of replacement cells and tissues to treat diseases including Parkinson's, stroke, heart disease and diabetes. This prospect is an exciting one, but significant technical hurdles remain that will only be overcome through years of intensive research.

Stem cells could be used to study disease

In many cases it is difficult to obtain the cells that are damaged in a disease, and to study them in detail. Stem cells, either carrying the disease gene or engineered to contain disease genes, offer a viable alternative. Scientists could use stem cells to model disease processes in the laboratory, and better understand what goes wrong.

Stem cells could provide a resource for testing new medical treatments

New medications could be tested for safety on in large specialized cells generated numbers from stem cell lines – reducing the need for animal testing. Other kinds of cell lines are already used in this way. Cancer cell lines, for example, are used to screen potential anti-tumor drugs.

Future Perspectives of Stem Cell Research

- Low blood supply [24]: Now the method to produce large numbers of Red blood cells has been developed. In this method precursor Red blood cells, called hematopoietic stem cells are grown together with stromal cells, creating an environment that mimic the conditions of bone marrow, the natural site of red blood cell growth. Erythropoietin, a growth factor, is added coaxing the stem cells to complete terminal differentiation to red blood cells. Further research into this technique will have potential benefits to gene therapy& blood transfusion.
- Baldness: Hair follicles also contain stem cells, and some researchers predict research on these follicle. Stem cell may lead to successes in treating baldness through "hair multi-

placation" and known as "hair cloning" as early 2011. This treatment is expected to work through taking stem cells from existing follicles, multiplying them in cultures, and implanting the new follicle cells which have shrunk during the ageing process, which in turn respond to these signals by regenerating and once again making healthy air. [25]

- Missing teeth: The work on tooth generation has reached to a stage that it will be available to the general population in that decade. In theory, stem cells taken from the patient could be coaxed in the lab into turning into a tooth bud which, when implanted in the gums, will give rise to a new tooth, which would be expected to take two months to grow. It will fuse with jawbones and release chemicals that encourage nerve and blood vessels to connect with it.
- Deafness: Those have been success in regrowing cochlear hair cells with the use of stem cells.
- Blindness and vision improvement: [24] Since 2003 research have successfully transplanted retinal stem cells into damaged eye to restore vision. Using embryonic stem cells, scientists become able to grow the sheet of top potent stem cells in the laboratory. When these sheets are transplanted over the damaged retina, the stem cells stimulate neural repair, eventually restoring vision. The group led by Dr. Sheraz Daya was able to successfully use adult stem cells obtained from the patient, a relative, or even a cadaver. Further rounds of trials are ongoing.
- Bone regenerations: Mesenchymal stem cells can be pumped and cutters expanded from animals and human and have been shown to regenerate functional tissue when delivered to the site of musculo-skeletal defects in experimental animals. Mesenchymal stem cells can regenerate bone in a clinically significant osseous defect and may therefore provide an alternative to autogenous bone grafts.
- Diabetes Type I: In people who suffer from type I diabetes, the cells of the pancreas that normally produce insulin are destroyed by the patient's own immune system. New studies indicate that it may be possible to direct the differentiation of human embryonic stem cells in the cell culture to form insulin-producing cells that eventually could be used in transplantation therapy for diabetics.
- Graft vs. host disease and Crohn's disease: Phase III clinical trials expected to end in second-quarter 2008 were conducted by Osiris Therapeutics using their in-development product Prochymal, derived from adult bone marrow. The target disorders of this therapeutic are graft-versus-host disease and Crohn's disease.[24]

- Wound healing: In one experimental method in regenerative medicine, stem cells are used to stimulate the growth of human tissues. In an adult, wounded tissue is most often replaced by scar tissue, which is characterized in the skin by disorganized collagen structure, loss of hair follicles and irregular vascular structure. In the case of wounded fetal tissue, however, wounded tissue is replaced with normal tissue through the activity of stem cells.[25] A possible method for tissue regeneration in adults is to place adult stem cell "seeds" inside a tissue bed "soil" in a wound bed and allow the stem cells to stimulate differentiation in the tissue bed cells. This method elicits a regenerative response more similar to fetal wound healing than adult scar tissue formation.[23] Researchers are still investigating different aspects of the "soil" tissue that are conducive to regeneration.[25]

CONCLUSION

Stem cells pose a bright future for the therapeutic world by promising treatment options for the diseases which are considered as noncurable now a days. However, because of significant peri and post-transplant morbidity and mortality further research and trials are required to refine and optimize conditioning regimens and modalities of supportive care. By virtue of funding of stem cell research, we hope to see new horizon of therapeutics in the form of organ development and replacement of lost tissue such as hairs, tooth, retina and cochlear cells.

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