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STEM CELLS: A NEW PARADIGM

Abhishek Kumar Singh*, Swapnil S Khairnar[1], Avinash B. Darekar[1] and Ravindranath B. Saudagar[2]

*,[1]Department of Pharmaceutics, KCT'S R.G.Sapkal College of Pharmacy, Anjaneri, Nashik, 422 213, Maharashtra, India.

[2]Department of Pharmaceutical Chemistry, KCT'S R.G.Sapkal College of Pharmacy, Anjaneri, Nashik, 422 213. Maharashtra, India.

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***Correspondence for Author**
Abhishek Kumar Singh
Department of Pharmaceutics, KCT'S R.G.Sapkal College of Pharmacy, Anjaneri, Nashik, 422 213, Maharashtra, India.

ABSTRACT

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 which 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 and wnt geneis 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. Cell based therapies might become commercial in coming years.

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

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.[1,2] Stem cells are primal cells which are considered to be progenitor of more than 200 cell types present in adult body. All stem cells are unspecialized (undifferentiated) cells that are characteristically of the same family type (lineage). They retain the ability to divide throughout life and give rise to cells that can become highly specialized and take the place of cells that die or are lost. The rigorous definition of a stem cell requires that it possesses two properties Self renewal and Unlimited potency Self renewal means the ability to go through numerous cycles of cell division while maintaining the undifferentiated state. Unlimited potency means the capacity to differentiate into any mature cell type. In a strict sense, this makes stem cells either totipotent or pleuripotent. Multipotent and unipotent are also described to define stem cell potency. These properties can be illustrated in vitro using methods such as clonogenic arrays where the progeny of cells is characterized.

Two broad categories of stem cells exist: embryonic stem cells derived from blastocyst and adult stem cells which are found in adult tissue. In a developing embryo, stem cells are able to differentiate into all the specialized embryonic tissue. In adults, stem cells act as a repair system for the body replacing specialized damaged cells.

Source of Stem Cells

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 an invitro fertilization clinicals 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. 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.

Type of Adult Stem Cells

Stem cells with broad differentiation potential appear to exist in adult bone marrow and, perhaps, in other tissues as well. Stem cells located outside of the bone marrow are generally referred to as tissue stem cells. Such stem cells are located in sites called niches[15](niche- a specialized cellular environment that provides stem cells with the support needed for self-renewal. Straddling and Xie characterized the niche cells that govern the production of Drosophila embryonic germline stem cells- those cells in the ovary that are the earliest precursors to eggs. According to the scientists, their findings offer a potentially valuable (model to explore how stem cells are regulated in vivo). For instance in the gastrointestinal tract they are located at isthmus of stomach glands and at the base of crypts of the colon. Niches have been identified in other tissues, such as the bulge area of hair follicles and the limbus of cornea.[16,17,18]

Bone marrow stem cells

Bone marrow is the major source of adult stem cells. There are mainly two types of marrow stem cells:

1. **Bone marrow hematopoietic stem cells**

Hematopoietic stem cells are stem cells and the early precursor cells which give rise to all the blood cell types that includes both the myeloid (monocytes and macrophages, neutrophils, basophils, eosinophils, erythrocytes, megakaryocytes/platelets and some dendritic cells) and lymphoid lineages (T-cells, B-cells, NK cells, some dendritic cells). Hematopoietic stem cells generate all the blood cells and can reconstitute the bone marrow after depletion caused by disease or irradiation.[19,20]

2. **Bone marrow stromal stem cells**

Mammary stem cellsprovide the source of cells for growth of mammary gland during puberty and gestation and play an important role in carcinogenesis of breast[21]A single such cell can give rise to both luminal and myoepithelial cell types of the gland and has been shown to regenerate the entire organ in mouse.[22]

3. **Mesenchymal stem cells**

It is an multipotent stem cells that can differentiate into variety of cell types in vitro or vivo include osteoblasts, chandrocytes, myocytes, adipocytes, neuronal cells, and described lately, into beta pancreatic ielet cells. These cells have been classically obtained from the bone marrow, and mesenchymal stem cells.

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 granulocytecolony 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 todayUses 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 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. can some time refer to marrow stromal cells. While the terms mesenchymal stem cell and stromal cells have been used interchangeably, they are increasingly recognized as separate entities as: Mesenchymal stem cells can encompass multipotent cells derived from other non-marrow tissues, such as adult muscle side population cells or the Wharton's jelly present in the umbilical card; and Stromal cells on a highly heterogenous cells population consist of multiple cell types with different potential for proliferation and differentiations. In contrast, Mesenchymal stem cells represent a more homogenous subpopulation of mononuclear progenitor cells possessing stem cells features specific cell surface markers.

Neural stem cells

The existence of stem cells in the adult brain has been postulated following the discovery that the process of neurogenesis, birth of new neurons, continues into adulthood in rats. Normally adult neurogenesis is restricted to the subventriculare zone, which lines the lateral ventricles of the brain, and the dentate gyrus of the hippocampal formations. Although the generator of new neurons in the hippocampus is well established, the presence of true self renewing stem cells there has been debated.[23] Neural stem cells are commonly cultured in vitro as so called neurospheres floating heterogenous aggregates of cells, containing a large proportion of stem cells.

Olfactory adult stem cells

Olfactory adult stem cells have been successfully harvested from the human olfactory mucosa cells, the lining of nose involved in the sense of smell.[5]

Adipose derived adult stem cells

These cells have also been isolated from human fat, usually by method of liposuction. This cell population seems to be similar in many ways to mesenchymal stem cells derived from bone marrow. Human adipose derived stem cells (ASC's) have been shown to differentiate in the lab into bone, cartilage, fat, muscle and might be able to differentiate into neurons, making them a possible source for future application in the clinic.[24,25]

Multipotent adult progenitor cells

The adult bone marrow also harbors a heterogeneous population of stem cells, which appear to have very broad developmental capabilities called multipotent adult progenitor cells. It has been proposed that multipotent adult progenitor cells constitute a population of stem cells derived from or closely related to embryonic stem cells. may be adult counterpart of embryonic stem cells.

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

These are

1. **Embryonic stem cells** It 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 [28] Skin cells from an immuno deficient mouse were used to generate cellular therapy that partially restored function in the mouse. This can also be used in treating human patient with immuno 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.

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[30,31] 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.[32,33,34]

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 Damage[8,35,36]

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 pro-drug into a chemotherapeutic agent. As a result, the injected substance was able to reduce tumor mass by 80 percent.[12,21]

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.[37]

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%.[14,38]

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[33,34].

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. Adult stem cells offer a unique alternative in that they may be isolated, studied, or manipulated without harming the donor. Currently, several obstacles for use of adult stem cells as therapy exist. First, the ability to identify most adult stem cells is impeded by lack of stem cell markers. Second, in vitro systems for manipulating adult stem cell populations are often not well defined. Finally, our understanding of how adult stem cells are regulated within their niche is in its infancy.

Future Perspectives of Stem Cell Research

Low blood supply: 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.[17]

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 jaw bones 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 [18]: 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

Ethical Concerns in Stem Cell Research

In the case of embryonic stem cell research, the end that scientists hope to achieve is the relief of human suffering. That this is a humanitarian and worthy end is not in dispute. The controversy is about the means, namely, the consumption of donated embryos. More

particularly, embryonic stem cell research and therapy would use donated embryos that, by virtue of donor instructions, will never enter a uterus. Is it permissible to use those means to that end? Our task is to decide how we should act toward an embryo, and whether we should recognize, as we do among adults, distinctions between embryos of various types and in various circumstances. We immediately encounter the question of what beings we should classify as "persons" for purposes of the duty not to kill persons. For one who concludes that we are not obliged to refrain from using embryos that will never enter a womb, embryonic stem cell research is a case of fostering a worthy end by using only nonpersons as means.

CONCLUSION

Stem cells pose a bright future for the therapeutic world by promising treatment options for the diseases which are considered as non curable 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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