

## BRIEF REVIEW OF STEM CELL THERAPY

Patil Bhagyashree R\*, Mulaje .Suraj.S<sup>1</sup>, O.G.Bhusnure<sup>2</sup>

<sup>\*,1,2</sup> Department of Quality Assurance, Maharashtra College of Pharmacy, Nilanga-413521

\*Corresponding Author Email: [bshreepatil30@gmail.com](mailto:bshreepatil30@gmail.com)

### ABSTRACT

*There is much to be investigated about the specific characteristics of stem cells and about the efficacy and safety of the new drugs based on this type of cells, both embryonic as adult stem cells, for several therapeutic indications (cardiovascular and ischemic diseases, diabetes, hematopoietic diseases, liver diseases). Stem cells have a capacity for self-renewal and capability of proliferation and differentiation to various cell lineages. They can be classified into embryonic stem cells (ESC) and non-embryonic stem cells (non-ESC). This review takes the origin of stem cells, their properties, characteristics, current research, and their potential applications. It also focuses on the various challenges and barriers that we have to surmount before translating laboratory results to successful clinical applications. Stem cell treatments are a type of intervention strategy that introduces new adult stem cells into damaged tissue in order to treat disease or injury. Stem cells are a relevant source of information about cellular differentiation, molecular processes and tissue homeostasis, but also one of the most putative biological tools to treat degenerative diseases.*

### KEY WORDS

*Stem cells, embryonic stem cell, treatments, future challenges.*

### INTRODUCTION

Cell therapy is based on transplantation of live cells into an organism in order to repair a tissue or restore lost or defective functions. Cells mainly used for such advanced therapies are stem cells, because of their ability to differentiate into the specific cells required for repairing damaged or defective tissues or cells

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. The regulators of stem cell growth at genomic and proteomic level are identified and we might be able to control stem cell in vitro.

Stem cells are unique in their ability to divide and regenerate themselves and in their ability to remain specialized or unspecialized in the tasks

of the human body. Because of these unique traits, these cells hold a great deal of promise in helping us learn about disease and develop treatments. Many diseases, such as cancer, are the result of uncontrolled cell division, so learning how and why stem cells divide so many times may unlock the mystery of those conditions. The stem cells' regenerative properties may prove useful in developing treatments for conditions including diabetes, heart disease, Parkinson's disease, spinal cord injuries and strokes

### What are stem cells?

Stem cells are primal cells which are considered to be progenitor of more than 200 cell types present in adult body.

A 'true stem cell' must be unspecialized clonogenic and capable of unlimited self-

renewal, a process during which a stem cell can divide symmetrically and give rise to two daughter stem cells. It is this capacity to self-renew over a prolonged period of time that ensures that stem cell populations last throughout the life of an organism. Stem cells are able to renew themselves and produce mature cells with specific characteristics and functions by differentiating in response to certain physiological stimuli.

#### **Definition of stem cell:**

Stem cells are biological cells occurs in all multicellular organism, it has ability of self renewal and unlimited potency. Stem cells should possess mainly two properties:-self renewal means cell division and another is potency means to differentiate into any mature cell type. Stem cells are broadly classified into two types:

#### **1) Embryonic stem cells**

#### **2) Adult stem cells.**

#### **Sources of stem cells:**

There can be two sources of stem cells – Autologous and Allogenic. Autologous embryonic stem cells generated through therapeutic cloning and highly plastic adult stem cells from the umbilical cord blood or bone marrow are promising candidates. Allogenic stem cells can be derived from marrow, peripheral blood, cord blood, family donors or HLA typed or untyped unrelated donors.

Two important heterogeneous populations of stem cells in the bone marrow include hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs). HSCs give rise to all the blood cell types including erythrocytes, monocytes, neutrophils, eosinophils, basophils. MSCs provide stromal support to the HSCs and are progenitor cells for types of cells such as osteoclasts, chondrocytes, myocytes, the another source of stem cell is also available that is xenogenic stem cell derived from different

species used for research purpose specially for human treatment Mostly stem cells intended for regenerative therapy are generally isolated from the patient's bone marrow or adipose tissue.

New sources of mesenchymal stem cells are currently being researched, including stem cells present in the skin and dermis which are of interest because of the ease at which they can be harvested with minimal risk to the animal. Hematopoietic stem cells have also been discovered to be travelling in the blood stream and possess equal differentiating ability as other mesenchymal stem cells; again with a very non-invasive harvesting technique. Research is currently underway to examine the differentiating capabilities of stem cells found in the umbilical cord, yolk sac and placenta of different animals.

#### **Types of stem cells:**

Stem cells are broadly classified into-embryonic stem cell and adult stem cell

#### **I. Embryonic stem cells:**

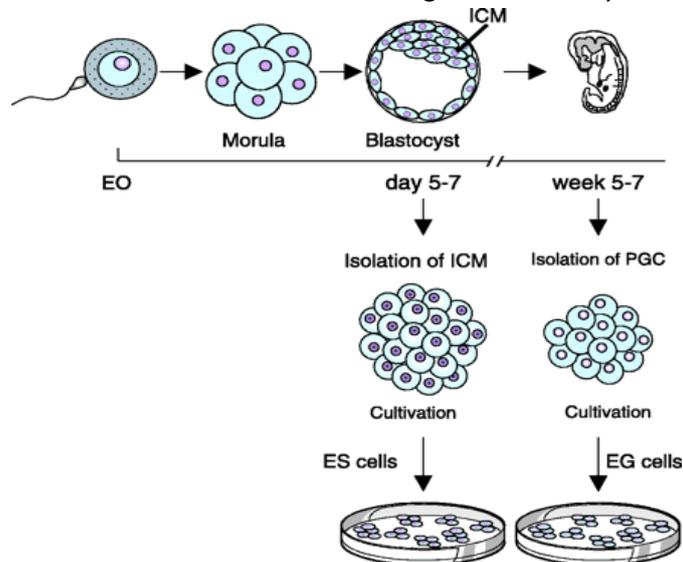
Different types of stem cells are distinguished based on their potential and source.

- 1) Totipotent embryonic cells
- 2) Pluripotent embryonic cells
- 3) multipotent embryonic cells
- 4) unipotent embryonic cells

Totipotent embryonic cells, which appear in the early stages of embryo development, before blastocyst formation, capable of forming a complete organism, as well as all intra and extra embryonic tissues. There are also pluripotent embryonic cells, which are able to differentiate into any type of cell, but not into the cells forming embryonic structures such as placenta and umbilical cord. Multipotent adult cells (such as hematopoietic cells, which may differentiate into platelets, red blood cells, or white blood cells) are partially specialized cells but are able to form a specific number of cell types.

Unipotent cells only differentiate into a single cell lineage, are found in the different body tissues, and their function is to act as cell reservoirs in the different tissues.

Germ stem cells are pluripotent embryonic stem cells derived from gonadal buds of the embryo which, after a normal embryonic development, will give rise to oocytes and spermatozoa



### Embryo development stage of stem cell

#### II. Adult stem cells:

Adult stem cells are undifferentiated cells found throughout the body that divide to replenish dying cells and regenerate damaged tissue. They are also known as somatic stem cells which can be found in children as well as adults. Adult stem cell possess two properties-renewal and multipotency. These cells occur in most tissues, including bone marrow, trabecular bone, periosteum, synovium, muscle, adipose tissue, breast gland, gastrointestinal tract, central nervous system, lung, peripheral blood, dermis, hair follicle, corneal limbus. Adult stem cells are mature undifferentiated cells that are found in specific tissues or organs. These cells remain present throughout the life of the organism. The main characteristic of adult stem cells is their ability of differentiating into mature phenotypes and being completely integrated into a specific tissue. Adult stem cell can be classified into different types, these are:-

- 1) Bone marrow derived stem cell
  - Hematopoietic stem cell

- Mesenchymal stem cell

- 2) Adipose tissue derive stem cell
- 3) Neural stem cell

- 1) Bone marrow derived stem cell:-it is the major source of adult stem cells  
 hematopoietic stem cell: - HSCs are involved in the production of blood cells in a process called haematopoiesis. These cells are not capable of differentiating into cells of any other tissue. They give rise to all the blood cells in the human body.. Only 8-10% of these stem cells are able to divide every day for the entire life of the animal. The remaining majority have a reduced ability to proliferate over months.
- 2) Mesenchymal stem cell:- mesenchymal stem cells (MSCs), which are of a mesodermal origin and have been isolated from bone marrow, umbilical cord blood, muscle, bone, cartilage, and adipose tissue. Mesenchymal stem cells can encompass multipotent cells ) from other nonmarrow 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. MSCs can be a suitable source of stem cells for tissue repair and gene therapy. Colony formation and proliferation in vitro can be triggered by several mitogenic factors, such as platelet-derived growth factors (PDGF), epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), transforming growth factor-beta (TGF-β) and insulin growth factor-1 (IGF-I).

3) Adipose tissue derive stem cell:- These cells have also been isolated from human fat, usually by method of liposuction. These cells secrete many cytokines and growth

factors with anti-inflammatory, antiapoptotic, and immunomodulatory properties such as vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), and insulin-like growth factor-1 (IGF-1), involved in angiogenesis, healing, and tissue repair processes.

4) Neural stem cell: - Neuronal stem cells able to replace damaged neurons have been reported in the nervous system of birds, reptiles, mammals, and humans. They are located in the dentate fascia of hippocampus and the subventricular area of lateral ventricles. Neural stem cells are commonly cultured in vitro as so called neurospheres – floating heterogenous aggregates of cells, containing a large proportion of stem cells.

Other types of stem cells are also present, these are such as skin and muscle stem cells, are unipotent in nature.

SOURCE	CELL TYPE	POTENTIAL MECHANISM OF ACTION	POTENTIAL EFFECTS
Blastula	Embryonic stem cells	Differentiation into cardiomyocytes	Direct contribution to contractility
Skin fibroblasts	Embryonic stem cells	Differentiation into cardiomyocytes	Remodelling of electrical properties
Heart	Cardiac stem cells	Differentiation into endothelial cells	Remodelling of infarcts and angiogenesis
Blood	Endothelial progenitor cells	Differentiation into smooth muscle cells	Remodelling of extracellular matrix
Bone marrow	Endothelial progenitor cells	Differentiation into smooth muscle cells	Contribution to mechanical properties of scar
Fat	Mesenchymal stem cells	Paracrine effects	Activation of endogenous stem cells

**Different types of stem cell**

**STEM CELL TREATMENTS IN VARIOUS DISEASES -**

**Brain damage**

Brain damages like stroke and traumatic brain injury causes cell death and characterized by a loss of neurons and oligodendrocytes within the brain. Healthy adult brains contain neural stem cells which divide to maintain general stem cell

numbers, or become progenitor cells. In healthy adult animals, progenitor cells migrate within the brain and function primarily to maintain neuron populations for olfaction. This system appears to be regulated by growth factors and can increase the rate at which new brain matter is formed in case of pregnancy and after injury. Stem cells

may also be used to treat brain degeneration, such as in Parkinson's and Alzheimer's disease.

### **Cancer**

Research in this area is still at an early stage. Using conventional techniques, cancer type like brain cancer is difficult to treat because it spreads so rapidly. The development of gene therapy strategies for treatment of intra-cranial tumours shown to be successful in the treatment of some dogs. The stem cells neither differentiated nor turned tumorigenic. Some researchers believe that the key to finding a cure for cancer is to inhibit proliferation of cancer stem cells. Accordingly, current cancer treatments are designed to kill cancer cells. However, conventional chemotherapy treatments cannot discriminate between cancerous cells and others. Stem cell therapies may serve as potential treatments for cancer. Research on treating Lymphoma using adult stem cells is underway and has had human trials. Essentially, chemotherapy is used to completely destroy the patient's own lymphocytes, and stem cells injected, eventually replacing the immune system of the patient with that of the healthy donor.

### **Heart damage**

After conducting several clinical trials targeting heart diseases, scientists and researchers have shown that adult stem cell therapy is safe, effective, and equally efficient in treating old and recent infarcts. While initial animal studies demonstrated remarkable therapeutic effects, later clinical trials achieved only modest, though statistically significant, improvements. Possible reasons for this discrepancy are patient age, timing of treatment and the recent occurrence of a myocardial infarction. These obstacles may be bypassed by additional treatments to the transplanted stem cells or the patient which increase the effectiveness of the treatment or by optimizing the methodology.. Stem cell therapy

for treatment of myocardial infarction usually makes use of autologous bone marrow stem cells, however other types of adult stem cells may be used, such as adipose-derived stem cells.

### **Blindness and vision impairment**

Since 2003, researchers have successfully transplanted corneal stem cells into damaged eyes to restore vision. "Sheets of retinal cells used by the team are harvested from aborted fetuses, which some people find objectionable." When these sheets are transplanted over the damaged cornea, the stem cells stimulate renewed repair, eventually restore vision. 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 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. In January 2012, The Lancet published a paper<sup>1</sup> by Dr. Steven Schwartz, at UCLA's Jules Stein Eye Institute, reporting two women who had gone legally blind from macular degeneration had dramatic improvements in their vision after retinal injections of human embryonic stem cells. A team of doctors lead by Dr. Virender Singh Sangwan, have developed a lab free technique of regenerating stem cells using tea bag or sprinkler approach.

### **Diabetes**

Diabetes patients lose the function of insulin-producing beta cells within the pancreas. Human embryonic stem cells may be grown in cell culture and stimulated to form insulin-producing cells that can be transplanted into the patient. However, clinical success is highly dependent on the development of the following procedures:

- Transplanted cells should proliferate

- Transplanted cells should differentiate in a site-specific manner
- Transplanted cells should survive in the recipient (prevention of transplant rejection)
- Transplanted cells should integrate within the targeted tissue
- Transplanted cells should integrate into the host circuitry and restore function

**Applications of stem cells:-**

There are different application in different forms

1. In tissue engineering:- Tissue engineering is an interdisciplinary field that applies the principles of engineering and the life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function.
2. In regenerative medicine:-this study helps in formation of new tissues for the replacement of lost or defective ones with using stem technology and tissue engineering.
3. in clinical application:-in this, helping for treatment of different human diseases that is, heart disease, spinal cord disease, cancer, brain damage and also used in veterinary application.
4. Current status of stem cell therapy: - An analysis of the drivers explains the factors for growth of the industry that include favourable regulatory environment, high patient population, stem cell application in drug development, rising consumer awareness, a rise in medical tourism and an increase in research and development expenditure to ensure stem cell therapy as a viable treatment for the numerous diseases. The key challenges include high cost of therapy; capital intensive market and high development costs of stem cell resulting in slow progress of the market.
5. The report provides a section on the recent developments that have taken place in the

stem cell research followed by a section on strategic recommendations created after a thorough analysis of the industry. The strategic recommendations section focuses on some effective strategic decisions which can be taken up by companies to increase their market shares.

**Future challenges of stem cell:**

Embryonic stem cells are naturally programmed to divide continuously and remain undifferentiated. To be used successfully in therapies, embryonic stem cells must be directed to differentiate into the desired type of tissue and ultimately stop dividing. Any undifferentiated embryonic stem cells that are placed in the body might continue to divide in an uncontrolled manner, forming tumors. Avoiding tumor growth is crucial to the success of stem cell therapies. Human embryonic stem cells have the remarkable capacity to mature into all of the 200 kinds of cells that make up the human body: skin, bone, nerve, blood, heart, and so on. By this nature, the cells hold great promise for treating devastating diseases like Alzheimer's, Parkinson's, cancer, and diabetes. However, some consider human embryonic stem cell research controversial because, in some cases, the new stem cell lines are derived from frozen human embryos that have been donated for research. Scientists are still struggling to understand whether their developmental potential is equivalent to that of embryonic stem cells. Some studies have suggested that iPS cells have more fragile genomes or are more prone to DNA abnormalities than embryonic stem cells. This fragility could make them unsafe to use therapeutically. The bottom line, says Daley, is that research on both types of stem cells must continue, because it's too early to predict where the safest and most effective cell-based therapies will come from.

Stem cell therapy encompasses new technologies and therapies that aim to replace damaged cells with healthy new ones. Cells may be dysfunctional due to any number of reasons such as genetics, disease, injury or aging. Currently, stem cells offer the potential to treat cancer, Parkinson's disease, spinal cord injuries and diabetes, among other serious diseases. Unfortunately, there are several challenges faced by researchers that must be overcome before stem cell therapies can become a successful reality for those suffering from disease. Researchers do expect to eventually move beyond these challenges but the unfortunate reality is that those suffering from disease often have little time to wait for treatment.

### Identifying Stem Cells in Adult Tissues

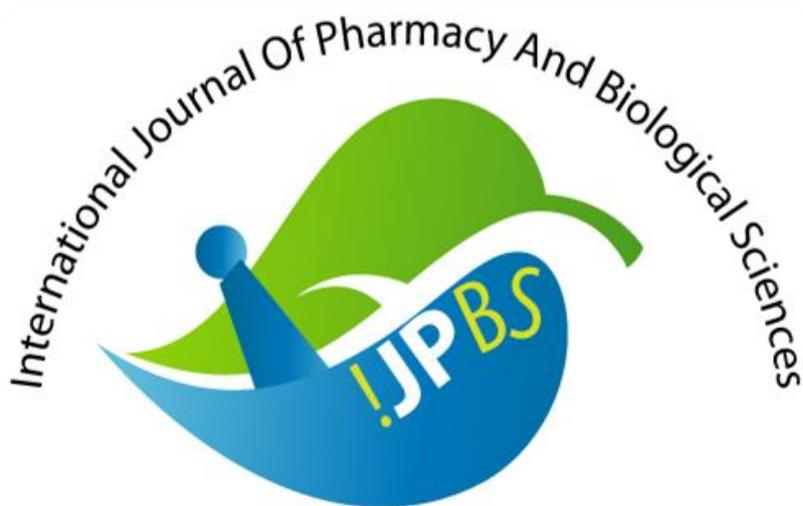
A major difficulty that scientists continue to encounter is the identification of stem cells in adult tissues. These tissues contain many different types of cells and an attempt to locate the often scarce numbers of stem cells in tissues that could contain thousands of different cells is difficult at best. The research involved is complex and even after cells are isolated, the process to successfully trigger differentiation into the desired cell type is another challenge for researchers. This requires an understanding of stem cell control and regulation that has yet to be fully gained. In addition, researchers must also use the correct laboratory medium, or solution, to coax the growth and this has proven to be difficult.

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**\*Corresponding Author:****Patil Bhagyashree R\****Department of Quality Assurance,  
Maharashtra College of Pharmacy, Nilanga-413521*