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STEM CELL: PAST, PRESENT AND FUTURE A REVIEW

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ABSTRACT
In recent years, stem cell therapy has become a very promising and advance scientific research topic. The development of treatment methods has evoked great expectations. This paper is review focused on the discovery of different steam cell and the potential the therapies based on these cells. The genesis of steam cell is followed by laboratory steps of controlled steam cell culturing and derivation. Quality control and teratoma formation assays are important procedures in assessing the properties of the steam cells tested. Derivation methods and the utilization of culturing media are crucial to set proper environmental conditions for of steam tissue applications, the use of graphene scaffolds and the potential of extracellular vesicle- based therapies require attention due to their versatility. The review is summarized challenges that stem cell therapy must overcome to be accepted worldwide. A wide variety of possibilities makes this cutting-edge therapy a turning point in modern medicine, providing hope for untreatable disease.

KEYWORD: Stem cell, Human genetic, Stem cells types, Vesicle therapy.

INTRODUCTION

Stem cell is primal cell common to all multicellular organism 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 cell can form various types of tissue cell. 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. There can be to sources of stem cell- Autologous and Allogenic. Autologous embryonic stem cell generated through therapeutic cloning and highly plastic adult stem cell from the umbilical cord blood or bone marrow are promising candidates. Allogenic stem cell can be derived from marrow, peripheral blood, cord blood family donor or HLA typed or untyped unrelated donor. This article focuses on types of stem cell and stem cell regulation with enlightening comments on clinical application and future aspects.

TYPES OF STEM CELL

Stem cell is broadly classified into two categories: Embryonic stem cell (ESC) and adult stem cell (ASC).

Embryonic Stem Cell

These cells are also known as early stem cell. Embryonic stem cells are derived from embryos at a developmental stage before the time of implantation would normally occur in the uterus. This developmental stage in the blastocytes stage- 32 cell stage, from which these pluripotent cells can be isolated.

Pluripotency of embryonic stem cells: Embryonic stem cells can give rise to cells from embryos germ layers i.e. ectoderm, mesoderm and endoderm, even after being grown in culture for a long time. In other word they can develop into each of more than 220 cell types of the adult body when given the sufficient and necessary stimulation for a specific cell type. ES cells can be maintained in culture as undifferentiated cell lines or induced to differentiate into many different lineages. Pluripotency distinguishes ES cells from multipotent cells found in adults, which can only from a limited number of different cell types.

Adult Stem Cells

Adult stem cells are undifferentiated cell 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 adult.

Type of Stem Cell: 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 (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 are 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 cell 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 comea.

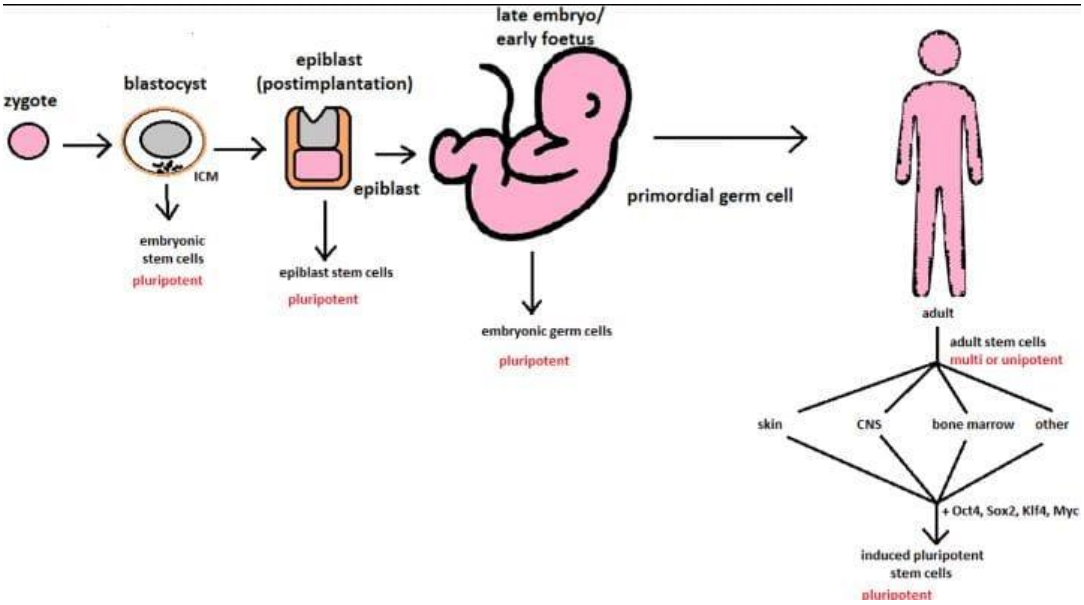
- **Bone marrow stem cell:** Bone marrow is the major source of adult stem cells. There are mainly two types of marrow stem cells: *bone marrow hematopoietic stem cells:* hematopoietic stem cells are stem cells and the early precursor cells which give rise to all the blood cell types that includes both the myeloid (monocytes and macrophages, neutrophils, basophils, eosinophils, erythrocytes, megakaryocytes/platelets and some dendritic cells) and lymphoid lineage (T-cells, B-cells, NK cells, some dendritic cells). Hematopoietic stem cells generate all the blood cells and can reconstitute bone marrow after depletion caused by disease or irradiation. *Bone marrow stomal stem cells*: Mammary stem cells provide the source of cells for growth of mammary gland during puberty and gestation and play an important role in carcinogenesis of breast. A single such a cell cane give rise to both luminal and myoepithelial cell types of the gland and has been shown to generate the entire organ in mouse.

- **Neural stem cells:** the existence of stem cell in the adult brain has been postulated following the discovery that the process of neurogenesis, birth of new neurons, continues into adulthood in rates. Normally adult neurogenesis is restricted to the subventricular zone, which lies the lateral ventricles of the brain, and 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. Neural stem cells are commonly culture in vitro as so called neurospheres -floating heterogenous aggregates of cell, containing a large proportion of stem cells.

- **Olfactory stem cells:** Olfactory adult stem cells have been successfully harvested from the human olfactory mucosa cell the lining of nose involve in the sense of smell.

- **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 cell derived from bone marrow. Human adipose derived stem cells (ASCs) 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 the clinic.



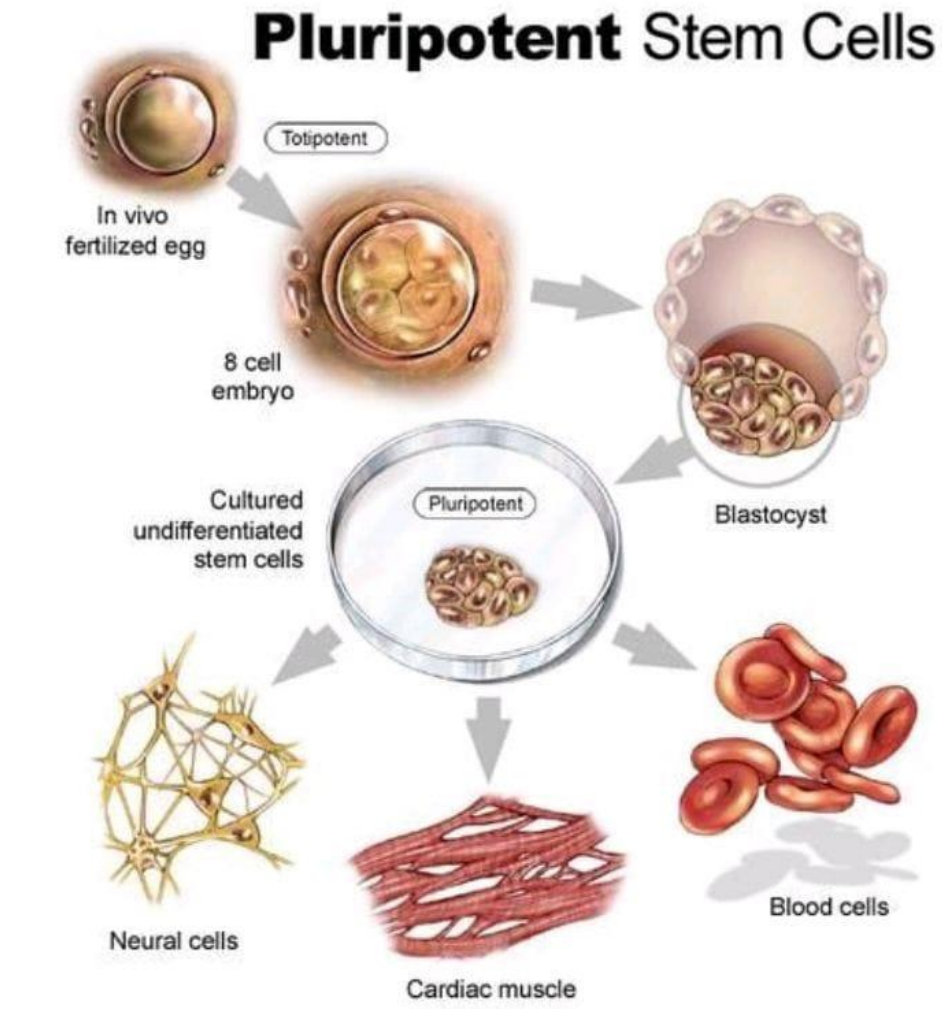
HUMAN PLURIPOTENT STEM CELL – BASED THERAPY: A GROWING GIANT

The discovery of hPSCs, including human embryonic stem cells (hESCs) and human induced pluripotent stem cell (hiPSCs), has revolutionized stem cell research and cell-based therapy. hESCs were first isolated from blastocyst-stage embryos in 1998, followed by breakthrough reprogramming research that con-verted somatic cell into hiPSCs using just four genetic factors. Methods have been developed to maintain these cells

long-term in vitro and initiate their differentiation into a wide variety of cell types, opening a new era in regenerative medicine, particularly cell therapy to replace lost or damaged tissue.

History of hPSCs

hPSCs are defined as self -renewable cell types that confer the ability to differentiate into various cellular phenotypes of the human body, including three germ layers. Historically, the first pluripotent cell lines to be generated were embryonic carcinoma (EC) cell lines established from human germ cell tumors and murine undifferentiated compartments. Although EC cell are a powerful tool in vitro, these cells are not suitable for clinical applications due to their cancer-derived origin and aneuploidy genotype. The first murine ESCs were established in 1981 based on the culture techniques obtained from EC research. Murine ESCs are derived from the inner cell mass (ICM) of the preimplantation blastocyst, a unique biological structure that contains outer trophoblast layers that give rise to the placenta and ICM. In vivo ESCs only exist for a short period during the embryo's development, and they can be isolated and maintained indefinitely in vitro in an undifferentiated state.



MESENCHYMAL STEM/STROMAL CELL-BASED THERPY: IS IT TIME TO CONCIDER THEIR ORIGIN TOWARD TARGETED THERAPY?

Approximately 55 years ago, fibroblast-like, plastic-adherent cells, later named mesenchymal stem cells (MSCs) by Arnold L. Caplan, were discovered for the first time in mouse bone marrow (BM) and were later demonstrated to be able to from colony-like structures, proliferate and differentiate into bone/ reticular tissue, cartilage, and fate. Protocols were subsequently established to directly culture this subpopulation of stromal cells from BM in vitro and to stimulate their differentiation into adipocytes, chondroblasts, and osteoblasts. Since then, MSCs have been found in and derived from different human tissue sources, including adipose tissue (AT), the umbilical cord (UC), UC blood, the placenta, dental pulp, amniotic fluid, etc. To

standardize and define MSCs, the international society for Cell and Gene Therapy (ISCT) set minimal identification criteria for MSCs derived from multiple tissue sources. Among them, MSCs derived from AT, BM and UC are the most commonly studied MSCs in human clinical trials, and they constitute the three major tissue sources of MSCs that will be discussed in this review.

The discovery of MSCs opened an era during which preclinical studies and clinical trials have been performed to assess the safety and efficacy of MSCs in the treatment of various diseases. The major conclusion of these studies and trials is that MSC-based therapy id safe, although the outcomes have usually been eighter neutral or at best marginally positive in terms of the clinically relevant end points regardless of MSC tissue origin, route of infusion, dose, administration duration, and preconditioning. It is important to note that a solid background of knowledge has been generated from all these studies that has fueled the recent translational research in MSC-based therapy. As MSCs have been intensively studied over the last 55 years and have become the subject of multiple reviews, systematic revies, and meta-analyses, the objective of this paper is not to duplicate these publications. Rather, we will discuss the questions that both clinicians and researchers are currently exploring with regard to MSC-based therapy, diligently seeking answers to the following

- "With a solid body of data supporting their safety profiles derived from both preclinical and clinical studies, dose the tissue origin of MSCs also play a role in their downstream clinical applications in the treatment of different human diseases?"

- "Do MSCs derived from AT, BM, and US exhibit similar efficacy in the treatment of neurological diseases, metabolic/ endocrine-related disorders, reproductive dysfunction, skin burns, lung, fibrosis, pulmonary disease, and cardiovascular conditions?"

To answer these questions, we will first focus on the most recently published clinical data regarding these targeted conditions, including neurological disorders, pulmonary dysfunctions, metabolic/ endocrine-related diseases, to analyze the potential efficacy of MSCs derived from AT, BM, and UC Based on the level of clinical improvement and MSC sources.

Table 1. The reported clinical trials using MSCs from AT, BM, and UC in the treatment of brain-related injuries and neurological disorders

Year	Disease	MSC source	No. of MSC-treated patients	Efficacy
2022[206]	Acute ischemic stroke	AT-MSC	4	No significant improvement compared to placebo in mRS and NIHSS score.
2014[461]	Acute ischemic stroke	AT-MSC	10	Potential efficacy of intravenous administration of allogeneic AT-MSCs within the first 2 weeks of stroke.
2020[196]	Autism spectrum disorders	BM-MSC	254	After transplantation, 94.48% patients showed a positive change on ISAA (Indian Scale for Assessment of Autism) and 95.27% of patients showed an improved score on CARS (Childhood Autism Rating Scale) and 86 (86/86) patients showed improved brain activity through the FDG-PET CT scan
2020[201]	Autism spectrum disorders	UC-MSC	12	Six of 12 participants demonstrated improvement in at least two ASD-specific measures
2017[195]	Cerebral palsy	BM-MSC	35	Scores of A, B, C, D, E and total scores of GMFM and FMFM significant improvement compared to before transplantation and control group
2020[199]	Cerebral palsy	UC-MSC	19	The ADL, CFA, and GMFM-88 scores significant improvement compared to before transplantation and control group
2011[189]	Chronic stroke	BM-MSCs	12	A modest increase in Fugl Meyer and modified Barthel index score.
				Increase the number of cluster activation of Brodmann areas 4 and 6 after MSC infusion.
2019[192]	Chronic stroke	Allogeneic BM-MSCs	36	The treatment was safe and well-tolerated based on serial exams, electrograms, laboratory tests, and computed tomography scans of chest/abdomen/pelvis.
				All behavioral endpoints showed significant improvement over 12 months of follow-up.
2005[186]	Ischemic stroke	BM-MSCs	5	Improve motor functions in the MSC-treated group during the follow-up period with no statistical significance.
2010[187]	Ischemic stroke	BM-MSC	16	mRS score significant improvement over the control group
2011[188]	Ischemic stroke	BM-MSCs	12	Slight change in NIHSS and mean lesion volume after the first week of infusion.
				Slight improvement in mRS score.
2021[180]	Ischemic stroke	BM-MSC	39	lower extremity motor function significant improvement over the control group
2020[190]	Ischemic stroke	BM-MSC	16	Did not improve the Basel index, mRS, and NIHSS after 2 years post infusion.
				MSC-based therapy might improve motor performance and task-related primary motor cortex activity.
2022[191]	Ischemic stroke	BM-MSC	31	Significant improvement in motor functions in MSC group.
				In neuroimaging analysis, corticospinal tract and posterior limb of the internal capsule fractional anisotrophy did not reduced in the MSC group but significantly decreased in the control group 90 days post infusion.
				Interhemispheric connectivity and ipsilesional connectivity significantly increased in the MSC group.
2018[462]	Ischemic stroke	Allogeneic UC-MSC	10	A slight improvement in mRS and NIHSS score relative to baseline.
2013[203]	Spinal cord injury	UC-MSC	22	Treatment was effective in 13 of 22 patients in ASIA, and IANR-SCIFRS scores
2021[202]	Spinal cord injury	UC-MSC	41	Significant improvement compared to before transplantation in ASIA total score, pinprick score and light touch, IANR-SCIFRS total score and sphincter score
2009[463]	Spinal cord injury	BM-MSC	10	Improvement in ASIA score, SEP and EMG.
2012[464]	Spinal cord injury	BM-MSC	10	6/10 patients showed improvement of motor power of the upper extremities at a 6-month follow-up
				3/10 patients showed gradual improvement in activities of daily living.
				MRI showed reduction in cavity size and the presence of fiber-like slow signal intensity steaks.
2012[465]	Spinal cord injury	BM-MSC	5	Significant improvement was observed in patients with AIS grade B and C.
2013[466]	Spinal cord injury	BM-MSC	50	BM-MSC-treated patients combined with physical therapy showed functional improvement over the control group.
				At 18-month follow-up, 23/50 MSC-treated cases (46%) maintained functional improvement.

Stem Cell Therapy In The Past

With increasing knowledge of stem cells, the trend to utilize the endogenous repair mechanisms of the human body gained popularity. Cells, growth factors and other biological products, when present on the right side; at the right moment, stimulate the natural healing mechanisms of the body and aid in the management of health condition.

Thus, the advent of cell-based treatment heralded the start of a new era in **regenerative medicine.** Many tissues, including the embryo, umbilical cord, placenta, and adult body's master cells, responsible for homeostasis maintenance even in healthy individuals, cellular repair and regeneration of wounded tissues, and bodily development.

Stem Cell Therapy At Present

Of course, everyone is aware of the moral dilemmas surrounding the usage of embryonic stem cells and the tumour-forming problem they provide. Since the banking of umbilical cord stem cells is a relatively new practice, the bulk of us would not have access to this source of stem cells. Researchers began containing on adult stem cells, which may be produced from many human body tissues, after taking these factors into consideration. The usual sources include, among others, bone marrow, adipose tissue, peripheral blood, and teeth.

The chief advantage is that the source is autologous, the therapy is safe and is not associated with side effects. We have just begun to scrape the surface of the disorders that stem cells can be used to treat. Mankind is plagued by a number of health issues, including severe injuries, **diabetes**, arthritis, and other disorders connected to the nervous system.

Conventionally, one would be prescribed medications (often for prolonged periods or even for their lifetime) or be advised surgery. However, a patient's quality of life is jeopardized in a number of situations. The many functions of stem cells include regulating the immune system, improving the performance of other cells, and fostering an environment where healthy cells can flourish.

This allows for the less invasive molecular targeting of a wide range of illnesses. Although patients are now well aware of the advantages of cell-based treatment and regenerative medicine research and development.

Research advances pertaining to introducing products with cell and scaffold-based technology through tissue engineering are underway. The development of bioactive scaffolds that can enable the activation and differentiation of host stem cells at the appropriate place is underway. In the future, it will be feasible to employ native human habitats as a micro-niche or micro-environment to enhance the body's reaction to a given place.

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
- Cord blood stem cell transplant
- Autologous stem cell transplant
- Nonmyeloablative stem cell transplant

The Future Of Stem Cell Therapy

Another breakthrough in the field of cell-based therapy is immunotherapy which aims to utilize certain parts of a person's immune system and stimulate them to fight diseases such as cancer. It seems like we need to rewrite our understanding of need with molecular concepts going beyond today's cellular concept because the nanomolecular bioactive proteins lipid particles are playing a major role to produce nanoparticles. These growth factors, cytokines, chemokines, proteins, ligands, receptors, exosomes, receptor blockers, and antibodies are the future of medicine.

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