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Review Article

Stem Cells, Classifications and their Clinical Applications -

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ABSTRACT

Stem cells have unique characteristics, they are unspecialized cells; they can reproduce itself over and over again through asymmetric cell division. There are different kinds of stem cells which depend on their originality and/ or their potency. Cell therapy is an emerging form of treatment for several diseases. Stem cells have generated incredible interest for repairing failing tissues and organs, which appeared to be the only reasonable therapeutic strategy. They seem to represent a future powerful tool in regenerative medicine, therefore, this review article aimed to elucidate the different sources of stem cells and their clinical applications.

Keywords: Stem cell; Classifications; Differentiation; Clinical applications

ABBREVIATIONS

EG: Embryonic Germ; HSCs: Hepatic Stellate Cells; PGCs: Primordial Germline Cells

HIGHLIGHTS

- Stem cells have unique characteristics, they are unspecialized cells; they can reproduce itself over and over again through asymmetric cell division.
- There are different kinds of stem cells which depend on their originality and/ or their potency.
- Stem cell therapy has generated incredible interest for repairing failing tissues and organs.
- They seem to represent a future powerful tool in regenerative medicine.

INTRODUCTION

Stem cells have unparalleled characteristics. They are not specialized cells; they have the ability of self-replication and differentiation according to the suitable signal [1]. Stem cells can reproduce itself over and over again through asymmetric cell division, they can produce the newly produced offspring cells preserve the characteristics of the mother cell that has a different potency and lineage potential, such as a committed progenitor that transiently amplifies to make several offspring [2].

CLASSIFICATION AND SOURCES OF STEM CELLS

Stem cells can be classified according to their origin into four broad types, from embryos; from the fetus; from the infants and from the adult. Also, they can be classified according to their potency.

STEM CELLS CLASSIFICATION ACCORDING TO THEIR ORIGIN (FIGURE 1)

Embryonic Stem Cells (ESCs)

Embryonic stem cells: Embryonic stem cells are pluripotent, self-renewing cells that can be derived from both mouse or human blastocysts, they are taken from the very early stages of embryo development after 4-5 days after fertilization [3,4]. They can be stored in culture as undifferentiated cell lines and can be stimulated to differentiate into any cell line [5]. They can differentiate into endoderm, mesoderm, and ectoderm embryonic germ layers, and also any type of somatic cells. They, therefore, hold a great capacity in tissue regeneration therapy [6].

Embryonic Germ Stem Cells: Embryonic Germ (EG) cells are taken from the later stages of the embryo development cells. They are derived from Primordial Germline Cells (PGCs) in the

early development. They are mainly isolated from the fetal tissue in narrow-window timing [7]. The PGC-derived cells were pluripotent, although, it was not possible to demonstrate pluripotency by generating the formation of teratomas in mice [8].

Fetal stem cells: Fetal stem cells are primal cell types found in the organs of the fetuses. They are able to differentiate into two types of stem cells: pluripotent stem cells and hematopoietic stem cells. Neural crest stem cells, fetal hematopoietic stem cells and pancreatic islet cells have been isolated in the fetuses [9]. Human fetal stem cells have been used by many people, children and adults that are suffering from many of mankind's most devastating diseases [10].

Infant stem cell

Umbilical cord stem cells: Umbilical cord blood contains prevalent stem cells which differ from those of bone marrow and adult peripheral blood [11]. Cord blood stem cells have shown to be multipotent as it being able to differentiate into neurons and liver cells [11].

Wharton's jelly: Wharton's jelly, which is the umbilical cord matrix, is considered to be a source of mesenchymal stem cells. These cells express typical stem cell markers, can be propagated for long times and can be induced to differentiate *in vitro* into neurons [12].

Adult stem cell

Adult stem cells are any stem cells taken from mature tissue; they are found in the tissues of a fully developed child (whole embryo) or adult and can only produce a limited number of cell types. They have limited potential as compared to the stem cells that derived from embryos and fetuses because of the stage of development of these cells [13]. They play a vital role in tissue repair, regeneration; and they are referred to their tissue origin [14]. Bone marrow is an abundant source of adult stem cells [15].

Mesenchymal stem cells: Mesenchymal Stem Cells (MSCs) are a different population of cells with the potential to differentiate into various somatic lineages. They were at first described as adherent cells with a fibroblast-like appearance that can differentiate into osteocytes, chondrocytes, adipocytes, tenocytes and myocytes [16].

MSCs can be isolated from the bone marrow and readily discredited from the hematopoietic stem cells due to their plastic adherence [17]. They are used in tissue engineering and regenerative medicine [18]. They are character by long-storage without major loss of their potency [19].

Hematopoietic stem cells: Hematopoietic stem cells are cells having the self-renewing potential and the capacity to give rise to differentiated cells of all hematopoietic lineages. Therefore, they transplanted for complete healing of hematologic disorders and after high-dose chemotherapy against malignant diseases [20].

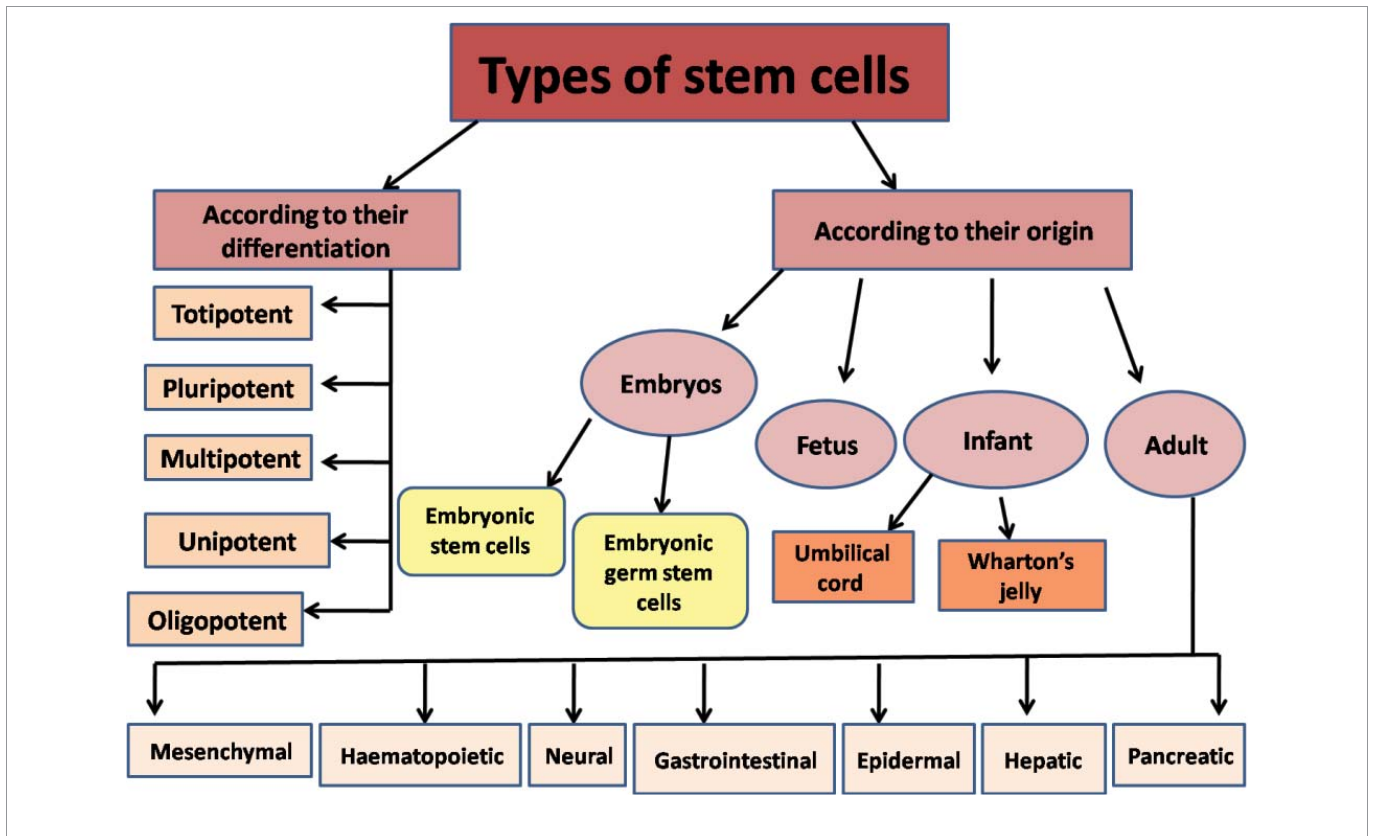


Figure 1: Classifications of stem cells.

Neural Stem Cells: Neural stem cells are multipotent and self-replication cells, they are established in specialized molecular microenvironments in the adult mammalian brain. They can display the potential role in cellular therapy of the brain [21].

Gastrointestinal stem cells: The stem cells of the gastrointestinal tract reside in a “niche” in the intestinal crypts and gastric glands. The mechanism and the direction of the diffusion of this converted clone in the gastrointestinal mucosa are hotly disputed, and the central to this case is the position and nature of the gastrointestinal stem cells [22].

Epidermal stem cells: The mammalian epidermis is a rapidly rejuvenating tissue that consists of three types of keratinocytes with varying differentiation potential: epidermal stem cells, Transiently Amplified Cells (TA cells) and terminally differentiated cells. The epidermal stem cells have free self-renewal power. They are establishing in the basal layer and remarkable in maintaining homeostasis and cellular regeneration of normal skin; wound healing and neoplasm formation, whereas TA cells, progeny of the epidermal stem cells, undergo terminal differentiation after 3–5 divisions. After division, TA cells leave the basal layer and move through the suprabasal layers to the tissue surface, where they are periodically shed as squames [23].

Hepatic stem cells: The liver has a strong regenerative capacity, utilizing different modes of regeneration according to the type and extent of the injury. Mature liver cells can propagate to replace the damaged tissue permit the recovery of the parenchymal function [24]. Chronic liver injury gives rise to a potential stem cell compartment which is located in the smallest branches of the intrahepatic biliary

tree being activated, which called oval cell ductular reaction. These oval cells are derived from the canal of Hering, which amplifies this biliary populations prior to these cells differentiate into hepatocytes. In the human liver, the organization of the biliary tree is different, with the canal of hering extending to the proximate third of the lobule and so apparently requiring a name change from oval cells to hepatic progenitor cells [25].

Pancreatic stem cells: Insulin-producing cells previously generated from pluripotent stem cells. The generation of these cells would provide a novel cell source for drug discovery and cell transplantation therapy in people suffering from diabetes [26]. Insulin-producing beta-cells turnover every 40-50 days by processes of apoptosis and the propagation and differentiation of the newly islet cells from progenitor epithelial cells, which are located in the pancreatic ducts [27].

Types of stem cells according to their differentiation

Stem cells can be classified according to their differentiation potential as a totipotent, pluripotent, multipotent, unipotent and oligopotent (Figure 1).

Totipotent stem cells: Totipotency means that it has the total potential to give rise to all types of cells. Totipotent is the capacity of a single cell to divide and differentiate into all cell types in an organism and produce fertile offspring. Oocytes and sperm are the best differentiated cells in our body and they are capable of forming any tissue in the body [28].

Pluripotent stem cells: Pluripotency is the ability of the cells to produce any type of cells in the organism. They have been derived



from the mouse embryo. All are capable of differentiating into cells representative of a variety of adult tissue types in various assays, including embryoid body, teratoma, and some can contribute to mouse development in chimeras. There are many differences being recognized among pluripotent stem cell types, such as their morphology, gene expression profiles and growth factor requirements [29].

Multipotent stem cells: Multipotency means to those cells that can only give rise to cells of the tissue from which they are isolated [30].

Unipotent stem cell: Adult stem cells are found in the tissues of the adults they produce a limited number of cell types and can repair damaged tissue by replacing specialized cells. Because of their restricted lineage, they were thought to be either multipotent, with the ability to differentiate into a limited range of cells or unipotent, with the ability to produce only one cell type [31].

Oligopotent stem cells: Oligopotency means to those cells that can differentiate into only a few cell types, like lymphoid or myeloid stem cells [32].

BIOLOGICAL PROPERTIES OF MSCS

Homing of MSCs

A stem cell may leave its niche and circulate in blood after particular stimuli [33]. The cell must be afterward attracted to another site, where under specific microenvironmental circumstances is able to enter its differentiation program [34]. MSCs were also described to locally migrate to injured sites to support the regeneration process. Such cases were documented in cartilage repair [35], muscle [36], and heart [37] regeneration, migration throughout for brain and cerebellum [38] and differentiation into osteoblasts in regenerating bone [39]. The homing capacity of MSCs may decrease after extensive culturing *in vitro* [40].

Differentiation potential of MSCs

Mesenchymal stem cells show a successful differentiation into a variety of cell lineages, including osteoblasts, chondrocytes, adipocytes, fibroblasts, myoblasts, cardiomyocytes, hepatocytes, tenocytes, cenocytes, and even neurons [41]. When MSCs are seeded at low density, they proliferate and secrete Dickkopf-related protein 1, which favors the undifferentiating phenotype of the cells. On the contrary, when the cells reach confluence, Wnt-5a expression abrogates the effect of Dickkopf-1 Dkk1 [42].

SOME OF THE CLINICAL APPLICATION OF STEM CELLS

Stem Cells and diabetes mellitus

Stem cells have generated incredible interest for repairing failing tissues and organs [43] (Table 1). Stem cell therapy has become a tantalizing idea to provide glucose-responsive insulin-producing cells to Type 1 diabetic patients as an alternative to islet transplantation [44]. Mesenchymal stem cells will grow and differentiate according to their environment. When MSCs injected into the pancreas *in vivo*, it is expected that MSCs will differentiate into pancreatic cells that have both exocrine and endocrine functions. Thus, transplantation of MSCs from bone marrow stem cells can repair the pancreas in its role to provide paracrine effects and other cell differentiation effects [45].

A beneficial effect of MSC transplantation on diabetes via a direct effect of differentiation to cells capable of producing insulin, or an

indirect effect of secretion of immune modulators, which prevent endogenous T cells from eliciting pancreatic β -cell destruction, or other as yet unknown factors, which influence insulin secretion or action [46].

Stem cell therapy and Parkinson's disease

Parkinson's disease (PD) is a widespread neurodegenerative disease that characterized by bradykinesia, rigidity, and tremor. The pathological causes of PD are due to the Decrease of Nigrostriatal Dopamine (DA) neurons, but neuronal degeneration also occurs in non-DA-ergic systems [47]. MSCs are capable of differentiating into tyrosine hydroxylase-positive neurons and can ameliorate motor performance in mice Parkinson's disease model [48]. Moreover, it has been demonstrated that cells with DA-ergic can be produced from both rat and human MSCs, and that transplantation of these cells showed an improvement of motor function in an animal model of PD [49].

Stem cells and heart disease

Physicians of cardiac disease looking forward a remedy for the patients who are suffering from the heart disease. Cardiac transfer of stem and progenitor cells can have an adequate effect on tissue perfusion and contractile performance of the injured heart. Stem cells have the potency to promote myocardial perfusion and contractile performance in patients who are suffering from acute myocardial infarction, advanced coronary artery disease, and chronic heart failure [50].

Autoimmune diseases

Autoimmune diseases are produced as a result of an immune response of the body versus the normal cells and tissues. According to their ability to modulate immune responses, MSCs have also been proposed as a treatment for autoimmune diseases. Patients who are suffering from severe autoimmune diseases do not respond to the standard therapy and often require autologous or allogeneic Hematopoietic Stem Cell Transplantation (HSCT) [51].

Liver diseases

Liver failure and cirrhosis occur as a result of a variety of chronic hepatic injuries. MSCs have the potential to be used for the treatment of liver diseases due to their regenerative potential and immunomodulatory properties. They display sequential and overlapping severe pathogenic processes that include severe inflammation, hepatocyte necrosis, and fibrosis/ cirrhosis, and carry a high mortality rate [52].

MSCs have been demonstrated to play an immune-modulatory role through producing inhibitory cytokines or inducing the development of regulatory T cells [53]. MSC therapy appears to be effective in regulating the immune response in tissue injury, transplantation, and autoimmunity in both animal models of liver disease and patients in clinical trials [54]. MSCs can also directly inhibit the activation of Hepatic Stellate Cells (HSCs), the main cell source of the extracellular matrix, via MSC-derived IL-10 and TNF- α , and may also induce Hepatic Stellate Cells (HSC) apoptosis via, in part, the Fas/ FasL pathway [55]. Notably, MSCs have the potential to differentiate into myofibroblasts, which act as scar-forming cells within the liver in certain settings.

Kidney disease

Mesenchymal stem cells can migrate to deteriorate kidney tissue where they can generate an array of anti-inflammatory cytokines and

Table 1: Clinical applications of stem cells.

source	Dosage	Disease	Route of administration	Conclusion
<ul style="list-style-type: none"> Bone marrow mesenchymal stem cells Insulin producing cells (IPCS) 	1x10 ⁵ MSCs cell / rat 1x10 ⁵ IPCs cell / rat	Diabetes mellitus Type I, Wistar rats	<ul style="list-style-type: none"> Tail vein injection 	Stem cells, which can differentiate into IPCs, would provide a potentially free source of islet cells for transplantation and mitigate the major limitations of availability and allogeneic rejection. Therefore the use of stem cells is becoming the most favorable therapy for DM [43].
Human umbilical cord blood-MS C (UCB-MS C)	-	APP and presenilin (PS1) double-transgenic mice	Hippocampus	Improved spatial learning and memory in Morris Water Maze tests Reduced A β load and tau hyperphosphorylation, inhibited proinflammatory cytokine release from microglia [57].
Bone marrow derived MSCs	1x 10 ⁶ cells per rat	Cirrhosis rats	intravenous infusion at the tail vein	The exploration of the therapeutic potential of mesenchymal stem cells on hepatic cirrhosis will benefit millions of people who suffer from the end-stage of chronic liver diseases [58].
Bone marrow MSCs	1.75x10 ⁵	The sterile testes in Wistar male rats Erectile Dysfunction in diabetic rats	injected into the left testis	Testis of host infertile rats accepted transplanted MSCs. The transplanted MSCs could differentiate into germinal cells in testicular seminiferous tubules [59]. <ul style="list-style-type: none"> Stem cell therapy can apparently improve the erectile function of diabetic rats [60]. The possible mechanism of this effect may include the increase of the content of smooth muscle and endothelium.
Bone marrow MSCs	10 rats received mesenchymal stem cells (2 x 10 ⁶ cells /rat), first dose (10 ⁶ cells/ rat) and after one week, rats received the second dose of cells (10 ⁶ cells/ rat).	Diabetes in male Sprague Dawley (S.D) rats	intravenous injection through penial vein per rat	the consequences of the present work uncovered that rodent bone marrow harbors cells that have the ability to recover the islets of Langerhans and differentiate into useful insulin-secreting cells fit for controlling hyperglycemia, hyperlipidemia, and diverse adjusted parameters in diabetic rats. This may be useful in the avoidance of diabetic complications [61].
bone marrow-derived MSC	1 x 10 ⁶ MSCs per rat	Infertility in male rats	----	MSCs have tremendous potential for regenerative medicine; MSCs/BM is capable of differentiating into germ cells and Leydig cells in the testis. MSCs modulated the decline of serum testosterone levels induced by the lead treated group (LN) and approached within control values, especially at 60 days. Because Leydig cells are responsible for testosterone production, stem cell transplantation may replace the need of life-long testosterone supplementation in male hypogonadism. In addition, MSCs modulated DNA apoptosis in sperm and testicular tissues. These results show that MSCs could be both a rich and functional source for the treatment of infertility [62].

chemokines that can alter the course of the injury. Mesenchymal stem cells are thought to elicit repair through paracrine and/ or endocrine mechanisms that mend the immune response resulting in tissue repair and cellular replacement [56].

CONCLUSION

A stem cell is a special type of the cell that has the ability to divide for unbounded periods of the time and to give rise to the mature and specialized cells that make up an organism. It considers a new strategy for repairing failing tissues, organs and may be in the future to provide solutions to many diseases.

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