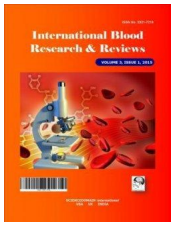

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Stem Cell Diversity and Applications in Therapy

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aim: In this review, we will discuss the different types of stem cells and their uses in therapies.
Introduction: Stem cells are cells produced during pregnancy, and have the ability to differentiate and self renew via stimulation. These cells are classified as totipotent, pluripotent and multipotent and totipotent has potency to differentiate in all types of cells.
Discussion: There are several types of stem cells such as embryonic, adult, mesenchymal and hematopoietic. Since these cells were discovered, they have been widely studied as an alternative treatment for various pathologies. The studies that have been conducted show that stem cells have potential in the treatment of diseases, particularly for the treatment of Parkinson's disease, Alzheimer's disease, heart disease and cancer.
Conclusion: The application of stem cells is a likely therapeutic alternative, despite their limitations. There is a need to extend research in this very promising area.

Keywords: Stem cells; pathologies; therapy.

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1. INTRODUCTION

During life, the tissues of the human body suffer many injuries which can be caused by disease or cell aging. However, research has been conducted in the areas of medicine, genetics and biotechnology over the years to enhance the recovery of health and increase life expectancy. In the last two decades, since the isolation of the first stem cell, researchers have conducted studies on the use of these cells in therapeutic interventions for a variety of diseases [1-2].

Stem cells develop in the embryonic stage, i.e. in the zygote after pronuclear fusion, and continue to be produced in the bone marrow into adulthood and remain in the body throughout the individual's life. They have the ability to proliferate and self-renew, and may also respond to different stimuli to produce different cell types which are capable of giving rise to tissues (Fig. 1) [3-5]. The characteristics of these cells have been the subject of study over the past two decades. They have been widely investigated in engineering applications, cell therapy, and as a source of tissue for transplantation [6,7].

Stem cells are classified according to their plasticity, i.e. their ability to differentiate into other cells. Totipotent cells can differentiate into any cell type in the body, while pluripotent cells have the capacity to differentiate into all kinds of cells, but cannot provide a complete organism. Multipotent cells, which are obtained from adult tissue, differ in the limited number of their lineage cells [4,8-10].

Stem cell therapy is based on replacing damaged cells with healthy cells generated from another organism. Stem cells are of fundamental importance for understanding the development of an organism and how health can be maintained following injury and disease over the course of a lifetime. Many patients end up needing complex procedures to repair damage or require organ transplantation [4]. However, organ transplant programs serve an only small number of patients, while the majority of patients continue to wait for another treatment option. In this context, stem cells may be a source of tissues for transplantation and a pathway to cell therapy for the treatment of various diseases [11-13].

One of the major fields of medicine today is regenerative medicine; it encompasses the treatment of various diseases such as leukemia, heart disease, kidney failure, and liver failure, among others. Studies show that many advances have been made in stem cell research in recent years because each cell type has a specific potential to be studied. Progenitor cell transplantation has improved the outcome of treatment as well as the regeneration of tissues in certain diseases [6,14]. The various types of stem cells can have many applications in biomedicine because they can be used in the repair of organs that have suffered injury, genetic analysis, and the study of cell differentiation; these are some of the ways to understand stem cells and their applications in therapy [15-17].

This mini review aims to discuss the different types of stem cells and their applications in therapy. Recent studies have shown the potential applications of these cells as a new alternative in the treatment of hepatic cirrhosis, since these cells have the capacity to differentiate into hepatocytes. Other studies have reported the use of stem cells to develop kidneys for transplant, which shows the potential of these cells for the treatment of various diseases [18,19].

2. TYPES OF STEM CELLS

In recent years, there has been a huge investment in stem cell research, since these cells have that ability to replace defective cells and differentiate into any cell type, or even merge with a diseased cell and make it healthier. Due to these features, since their discovery, these cells has been considered as an alternative for the treatment of various pathologies such as Chagas (Fig. 2) disease, Parkinson's disease, leukemia and others.

The whole issue around the use of stem cells is related to their therapeutic capacity which led to the authorization of the use of these cells in human medicine. However, there are many ethical questions related to the use of embryonic stem cells, because harvesting cells from the embryo leads to its destruction. Current biosafety law allows the use of cells from embryos produced by in vitro fertilization that are not implanted in the uterus because they are unviable or because they have been frozen for more than three years. The perspective on the use of these cells has been a source of hope for people with various incurable diseases and in need of organ donation. However, it is not a new science and although studies have shown the effectiveness of these cells, there have also been many failures, which compromises the use of

stem cells in therapy [21]. This minireview will discuss the cell types used in this type of therapy.

2.1 Embryonic Stem Cells

Embryonic stem cells develop from the inner cell mass (ICM) of an early embryo that is in the blastocyst stage. These cells undergo the process of differentiation to form the primitive ectoderm during gastrulation, differing into the three germ layers (ectoderm, mesoderm and endoderm) [23]. When blastocyst ICM cells are taken from their natural embryonic environment and placed in culture under the right conditions, they can multiply indefinitely in the laboratory, and studies have indicated the excellent potential of these cells to differentiate into a wide variety of adult cell types [24,25]. At the blastocyst stage, it is not yet defined as to what kind of tissue each cell will become, i.e. embryonic stem cells are undifferentiated and endowed with great plasticity [26].

Some high capacity embryonic stem cells can give rise to any cell type without, however, developing into a complete organism; they are classified as pluripotent, as they are not responsible for the development of extra embryonic tissues required to support the fetus [27]. Because of the origin of embryonic stem cells, they can be differentiated from other families of pluripotent human cells. Embryonic carcinoma cells (embryonic CC) are derived from undifferentiated stem cells of germ cell tumors located in rats and humans, while embryonic germ cells (embryonic GC) are derived from germ cells from the genital ridges of human or mouse fetuses. Since embryonic CC and GC are embryonic at an earlier stage of development, for this reason, their potential is limited compared with embryonic stem cells [24,28-29].

To initiate an in vitro differentiation program in embryonic stem cells, i.e. simulating the development of a pre-implanted embryo, it is necessary to promote cell aggregation, the result of which is the development of an embryonic mass containing undifferentiated cells. Using tools such as molecular, morphological and immunohistochemical analysis, different embryonic lineages that differentiate in the body have been observed, including neuronal, hematopoietic, endothelial, skeletal and cardiac muscle cells. However, to induce the directed differentiation of embryonic stem cells, it is extremely important to understand the regulators of differentiation [28,30].

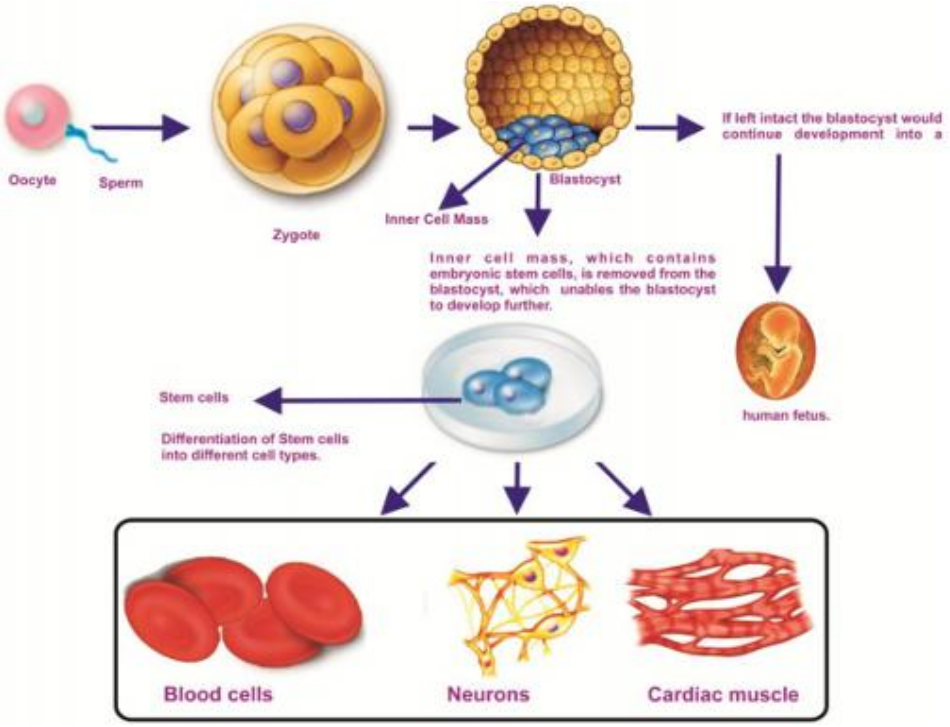

Fig. 1. The origin of stem cells and their ability to differentiate into various tissues [20]

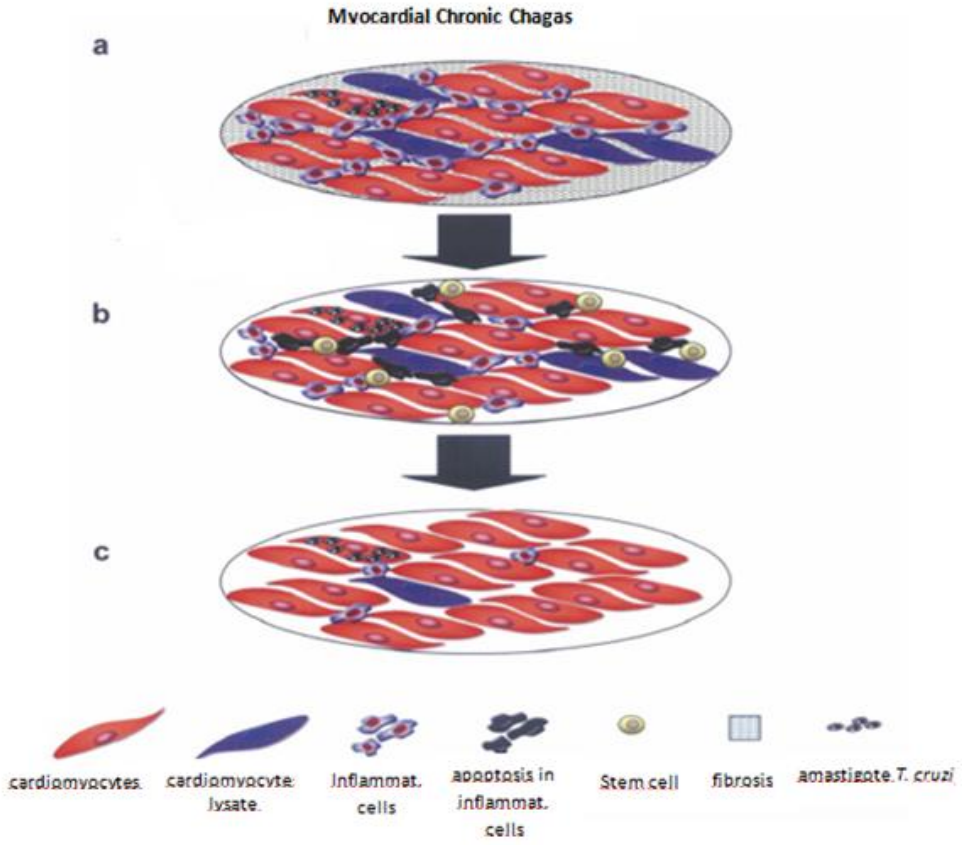

Fig. 2. Example of tissue repair resulting from transplanting bone marrow stem cells in chronic Chagas disease [22]

Currently, the prospects for regenerative medicine are enormous, but significant treatment still required considerable research. First, the safety of these cells must be considered because they can be dangerous. When used as a source of tissue to be transplanted, embryonic stem cells should be carefully differentiated to generate only the tissues of interest, otherwise they can differentiate in an uncontrolled manner leading to the formation of teratomas, which are tumors made up of many different tissues.

Studies on embryonic stem cells for applications in therapy are ongoing for many pathologies such as Parkinson's disease, aplastic anemia, spinal cord injury, macular degeneration and diabetes [31]. For the treatment of each disease, a specific cell lineage must be introduced, and compatibility between the donor and the recipient must be established. Alternatively, genetically identical cells may be more successful in the transplantation of embryonic stem cells. Using therapeutic cloning techniques, we can generate a cloned embryo of the patient and remove the embryonic stem cells [32]. This would lead to the creation of a tissue with 100% compatibility. However, it is noteworthy that, in people with an inherited deficiency, the compatibility issue would not be resolved because the cells of these individuals would also carry genetic defects and so could not generate healthy tissues for transplantation. This technique has been used in different types of animals [32].

2.2 Adult Stem Cells

Adult stem cells (adult SC) are present in the bone marrow, blood from the placenta and the umbilical cord of newborns and in several adult tissues. Recently, the pulp of baby teeth has been shown to be a source of adult SC [33,34]. Adult stem cells act in tissue homeostasis, producing new cells for physiological renewal or in response to injury. This cell category includes all types of stem cells after the blastocyst stage [35]. The bone marrow contains hematopoietic stem cells (hematopoietic SC) that originate blood cells (lymphocytes, erythrocytes, platelets,

etc.) as well as epithelial, muscle, neural, and mesenchymal tissue. It is believed that specific compartments exist for the stem cells of each tissue [36].

Adult SC have been known for some time and used since the 1950s in the treatment of different diseases that affect the hematopoietic system. These cells were observed to possess restricted potential for differentiation into only cells belonging to the tissue they live [31]. For example, hematopoietic stem cells are able to regenerate after the destruction of the very tissue (bone marrow) by irradiation, and liver cells proliferate in order to repair that organ. However, with progress in research, several studies have questioned this restricted potential and demonstrated a broad potential for differentiation, given the ability of these cells to give rise to different tissues. In a study on rats with Duchenne muscular dystrophy, a degenerative disease caused by a mutation in the dystrophin gene, the animals had their bone marrow regenerated after transplantation of normal mouse cells, and showed partial regeneration of muscle fibers containing an essential muscle protein. This study indicated that there was incorporation into the muscle tissue of animals affected by the disease after bone marrow transplant [37].

Autoimmune diseases have been treated with the transplantation of adult SC since 1996, with promising results suggesting long-lasting remission [16]. Systemic lupus erythematosus, multiple sclerosis, and rheumatoid arthritis have been treated with the transplantation of hematopoietic stem cells. Other diseases such as diabetes mellitus and Crohn's disease may soon begin to use this therapy [38].

The transplantation of adult SC has excellent potential, particularly since they are considered an alternative for the treatment of heart disease such as acute myocardial infarction [39]. In an animal study on acute myocardial infarction, after the introduction of SC in the infarcted wall after coronary joint, the formation of a new cardiac muscle was observed to take up 68% of the infarcted area of the ventricle, with improved ventricular function. This demonstrates that the use of these cells can promote an improved outcome of the disease [40].

2.3 Mesenchymal Stem Cells

Mesenchymal stem cells (mesenchymal SC) have generated interest regarding their therapeutic potential in the treatment of degenerative diseases. They are also called mesenchymal stromal cells, and are found in the bone marrow, adipose tissue, lung, Wharton's jelly, umbilical cord and placenta [41,42]. When mesenchymal SC are subjected to distinct stimuli in vitro, they gain the capacity to differentiate into osteogenic, chondrogenic, neurogenic, adipogenic and cardiogenic lineages [43,44,45]. The clinical applications of these cells has increased progressively in regenerative medicine because they are readily available without ethical problems associated with their use.

One study that investigated the use of transplanted mesenchymal SC in cardiac disease therapy showed a reduction in infarct size in the heart and improved cardiac function due to increased left ventricular ejection fraction; tissue repair was promoted by these cells [46]. Currently, there is evidence of mesenchymal SC activity in lung disease due to their ability to trigger protection mechanisms and to stimulate endogenous regeneration [47]. In orthopedics, mesenchymal SC help in the production of cartilage in tissues affected by erythematosus lupus or rheumatoid arthritis [48,49]. Mesenchymal SC are also active in the repair of epithelial injury due to burns and in vitiligo therapy [50,51]. Among several other clinical applications in regenerative medicine, mesenchymal SC have become an excellent therapeutic strategy for treating various diseases due to their multilineage differentiation capacity.

2.4 Corneal Stem Cells

The corneal epithelium acts as a protective barrier against microorganisms and liquid loss. The cells present in this epithelium undergo constant renewal, since the corneal epithelium constantly needs to be replaced [12,52]. The corneal tissue is formed in the fifth week of embryo development by the ectoderm. In the following weeks, the cell number increases, completing the formation of the ocular lens; cells then migrate into the space between the lens and the epithelium, becoming the corneal epithelium, which continues to develop until the eyelid is opened [53,54]. In the cell division of these cells, a daughter cell is generated that will establish stem cells while daughter cell temporarily amplified cells differentiate when stimulated in a specific tissue; they are located within the corneal limbus [12].

Lesions of the cornea are a major cause of vision loss. Treatment is based on corneal

transplantation, but this is not always effective, since the cells are absent in this environment in autoimmune disease and after burns. Recent studies have shown that donor stem cells present in the limbus can be grafted onto the cornea following injury [55]. The successful use of stem cells in the treatment of corneal diseases is associated with the survival of donor stem cells, since it is variable. Although the donated material has all the layers of limbal epithelial cells, survival also depends on the type of transplant, i.e. whether it is a straight graft or expanded cells in culture. New research shows that, to ensure long-term grafts, immunolocalization with markers such as p63 and K19 can be used to confirm the presence of stem cells of the cornea in cell culture [56-59].

In their study, Christovam et al. [60] used epithelial cells obtained from six donors that were grown in cell culture. It was found that these cells were able to proliferate and form cell colonies, thus maintaining the characteristics of progenitor cells, which suggests that these cells may be used to treat damage to and deficiencies of the cornea.

2.5 Hematopoietic Stem Cells

Multipotent hematopoietic stem cells are found in the bone marrow and are produced by the hematopoietic system. These cells are generated during embryonic development and can be found in the umbilical cord and in the fetal liver [62]. These cells have the ability to differentiate into mature hematopoietic stem cells with pluripontentiality and are capable of self-renewal in the long-term; when stimulated, these cells can generate functional heterogeneous cells of hematological lineages, with the potential to differentiate into all the hematopoietic system cells constantly, and are thus responsible for hematopoiesis throughout the life of the individual [62,63]. Hematopoietic stem cells in the adult individual can be found in the bone marrow and in small quantities in peripheral blood [62].

Because stem cells of the hematopoietic system present great potential for renewal as well as cellular differentiation capacity, considerable study has gone into developing therapeutic strategies for the treatment of many benign and malignant diseases by the transplantation of those cells. Nowadays, these transplants have become clinically feasible due to improved knowledge of the immune system, the patient's condition and the number of transfused cells, especially regarding the presence of granulocyte and myeloid progenitors, CD4+ CD8+, and CD34+ cells, as well as the expression of major histocompatibility complex (HLA), which have all led to an improved therapeutic response [61,64,65,66].

Transplantation of hematopoietic cells has increased considerably since 1997. However, therapy using stem cells requires cytochemical, cytomorphological, immunohistochemistry and immunophenotyping studies, as they are fundamental to characterize hematopoietic cells in order to provide the degree of cell differentiation required. Moreover, the plasticity of these cells allows them to differentiate into cells capable of replacing defective cells in the bone marrow. According to recent studies by Porada and collaborators [67], hematopoietic stem cells present in the peripheral blood have many advantages, since isolation is not invasive and stem cells are abundant. This method is increasingly used in the treatment of hematological disorders as well as metabolic diseases and immunodeficiencies, and has become an attractive alternative in transplantation [67].

2.6 Muscle Tissue Stem Cells

Muscle tissue is a highly specialized tissue formed during embryogenesis. Its stem cells are called satellite cells; they are mononuclear and possess multipotentiality and the ability to self-renew. They remain associated with muscle fibers after birth and play a role in development, muscle growth and muscle regeneration during the lifetime of the individual [68,69]. However, these cells are present in low numbers since they have limited proliferation capacity. These cells are located below the basal lamina of the muscle and are normally in a quiescent state. Satellite cells are activated by injury and trauma to the muscle. If satellite cells have problems in carrying out their function, this can lead to the loss of muscle recovery, especially in cases of muscle disease and old age [70-72].

Muscular dystrophies lead to the premature loss of function of self-renewing muscle cells. Recent research has focused on regenerative myogenesis, highlighting the role of these cells in the treatment of deficient muscle repair. However, satellite cells, due to their limited growth, require induction by growth factors such as IGF (Insulin-like growth factor), FGF-2

(fibroblast growth factor), HGF (Hepatocyte growth factor), which will induce these cells to exit the resting state and began to expand [70,72,73,74].

In a study by Shadrach and Wagers [70] on mice with Duchenne muscular dystrophy, following muscle stem cell transplantation, new cells were able to differentiate and contributed to the reconstruction of the injured muscle. It was observed that stem cell transplantation improved the function of grafted muscles, with increased contractile function of [skeletal muscle]. Moreover, the transplanted cells were capable of generating a reserve cells capable of differentiating through the need for cell regeneration. Although there is an effective treatment for muscular dystrophies, progress in the study of muscle stem cell transplantation is presented as a viable alternative in the treatment of these pathologies [74,75].

2.7 IPS Cell (Induced Pluripotent Stem Cells)

In 2006, was demonstrated that mature somatic cells can be reprogrammed to a pluripotent state by gene transfer, generating induced pluripotent stem (iPS) cells. Since that time, there has been an enormous increase in interest regarding the application of iPS cell technologies to medical science, in particular for regenerative medicine and human disease modeling [76]. iPS cells can be prepared from patients themselves and therefore great expectations have been placed on iPS cell technology because regenerative medicine can be implemented in the form of autografts presumably without any graft rejection reactions. Although there have been some controversies [77], the immunogenicity of terminally differentiated cells derived from iPS cells can be negligible [78-79]. Moreover, there has been substantial interest in the possibility of regenerative medicine without using the patient's own cells; that is, using iPS cell stocks that have been established from donor somatic cells that are homozygous at the three major human leukocyte antigen (HLA) gene loci and match the patient's HLA type [80]. The development of regenerative medicine using iPS cells is being pursued in Japan and the USA for the treatment of patients with retinal diseases, including age-related macular degeneration [81], spinal cord injuries [79], Parkinson's disease (PD) [82], corneal diseases [83], myocardial infarction [84], diseases that cause thrombocytopenia, including aplastic anemia and leukemia [85], as well as diseases such as multiple sclerosis (MS) and recessive dystrophic epidermolysis bullosa [86].

3. CONCLUSION

There have been many exciting advances in stem cell therapy. The ability to repair tissue without the use of potent drugs and without the dilemmas related to compatibility has led to great hope regarding the use of stem cells for the treatment of aggressive disease. Therefore, it is necessary to understand the intrinsic molecular mechanisms that enable stem cell maintenance or differentiation. In conclusion, the use of stem cells is a novel therapeutic alternative, despite their limitations and the need to extend research in this very promising area.

CONSENT

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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