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RESEARCH TITLE

Stem cell biology and the potential of various types for therapeutic applications: A Review

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Abstract

Stem cells are one of the most prominent scientific discoveries in the field of biomedicine, because they have unique abilities for self-division and differentiation into different types of specialized cells. This article deals with the historical path of the discovery of stem cells, starting from the first attempts to replace damaged tissue in the early twentieth century, through the first bone marrow transplants, the discovery of human leukocyte antigens (HLA), to the demonstration of the presence of stem cells in the bone marrow in mammals, and their classification into embryonic and adult cells. The article also reviews the clinical applications of stem cells in the treatment of diseases such as cancer, hemophilia and immunodeficiency, and highlights advances in conservation and freezing techniques that have opened up wide prospects for use in regenerative medicine and future treatments. The article aims to highlight the growing importance of stem cells in medical research and their pivotal role in the development of modern treatments.

Key Words: Stem cells, Regenerative medicine, Bone marrow, Self division, Therapeutic application.

Introduction

Stem cells have constituted a scientific and practical revolution, with the earliest research in this field dating back to the year 1900, when the idea first emerged of designing a healthy organ to replace a damaged or diseased one in a living organism. This concept paved the way for the discovery of what came to be known as stem cells. At the time, the failure of bone marrow physicians to treat leukemia patients through bone marrow grafting suggested the necessity of establishing specialized laboratories dedicated to the treatment of bone marrow diseases. The first allogeneic transfer of bone marrow between individuals of the same species was performed in France in 1950. In 1958, researcher Jean Dausset discovered the Human Leukocyte Antigen (HLA), which highlighted the presence of proteins on the surface of white blood cells, now known as HLA antigens. Subsequent studies demonstrated the role of these surface antigens in the immune system by identifying self and non-self cells (Thorsby, 2009).

In 1961, at the University of Toronto, researchers Ernest McCulloch and James Till confirmed the existence of stem cells in bone marrow and their capacity for self-renewal, through a study involving the transplantation of bone marrow from healthy mice into immunocompromised mice irradiated with radiation via tail vein injection. In these irradiated mice, a rare population of undifferentiated cells was observed migrating to the spleen. These cells divided and formed colonies comprising various types of blood cells. Furthermore, the transplantation of these colonies, formed in the spleens of irradiated mice, into other irradiated mice led to the formation of new colonies in their spleens as well. Based on the results of this experiment and subsequent ones, the researchers defined stem cells (Till and McCulloch, 1961) as undifferentiated cells capable of self-renewal, whose differentiation could be directed toward a desired cell type (Siminovitch et al., 1963).

The researchers also confirmed the existence of two types of stem cells in mammals: embryonic stem cells (ESCs), isolated from the inner cell mass of the blastocyst, and adult stem cells, which are found exclusively in mature and specialized tissues. Stem cells perform two essential functions: the first is their division and differentiation into various cell types during the early stages of embryonic development, and the second is the regeneration of aging tissues and the replacement of damaged ones throughout the individual's lifetime (Jaishankar and Vrana, 2009). By 1969, numerous laboratory experiments aimed to achieve successful transplantation between siblings in order to treat Severe Combined Immunodeficiency (SCID) (Kim et al., 2020). In 1973, the first heterogenetic transfer of bone marrow was performed. The year 1984 represented the peak of bone marrow research, and during the decade spanning 1980 to 1990, more than 16,000 transplantation procedures were conducted, most of which were recorded for the treatment of blood cancers, hemophilia, and Human Immunodeficiency Virus (HIV).

Since that time, stem cells have received considerable scientific interest, leading to the identification of numerous stem cell types, and enriching our understanding of cell biology and the molecular mechanisms responsible for cell division and differentiation. This progress has also enabled the preservation and cryogenic storage of stem cells for future use when needed, thus making their practical application possible in various medical and therapeutic fields.

1- **Classification of Stem Cells:**

Stem cells are classified either according to their differentiation potential or based on the source from which they are isolated. Based on their ability to differentiate into specific cell types, stem cells are divided into five groups:

-**Totipotent Stem Cells** are capable of differentiating into any type of cell and are the only cells that can give rise to a complete organism in addition to placental cells. Their source is the fertilized egg (zygote) and the cells resulting from its first division, starting from the two identical daughter cells.

-**Pluripotent Stem Cells** can differentiate into more than 200 different cell types and originate from the inner cell mass of the blastocyst.

-**Multipotent Stem Cells** are restricted to differentiating into a limited number of cell types. They are derived from the placenta and umbilical cord blood. These cells are mainly classified into three types based on the lineages they give rise to: hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), their counterparts in bone marrow known as stromal stem cells, and neural stem cells (NSCs).

-**Oligopotent stem cells:** cells that are restricted in their differentiation into two or more cell lines, such as neural stem cells in the brain.

-**Unipotent stem cells** differentiate into a single cell line, such as the primary gonads that produce sperm. In 2005, researcher Albert Lasker demonstrated that the genetic program of a cell could be reprogrammed into the genetic program of stem cells in a fertilized egg, which then give rise to embryonic stem cells. This suggested the possibility of converting specialized somatic cells into embryonic stem cells, using chemical and biological factors present in the fertilized egg. In 2006, researchers Yamanaki and Takahashi at Kyoto University in Japan were able to reprogram skin cells into unspecialized cells similar to embryonic cells. This was initially studied in mice in 2006, and then in humans for the first time in 2007 using four factors found in the fertilized egg: Oct3/4, c-Myc, Sox, and Klf (Takahashi et al., 2007). These and similar studies added a new group called **induced pluripotent stem cells (iPSCs)**, which are specialized and mature cells that can be reprogrammed and made to reverse their differentiation into cells with embryonic characteristics and capabilities. Stem cells are also classified according to their source into four main groups:

Embryonic Stem Cells (ESCs): These are isolated from the inner cell mass of blastocyst-stage embryos resulting from in vitro fertilization procedures. They are responsible for forming, developing, and growing the embryo. Embryonic stem cells were first isolated in the 1980s by independent research groups (Thomson et al., 1998).

Adult stem cells: They are found in the form of individual clusters in some adult tissues, and are responsible for maintaining tissues by renewing their cells that may be damaged as a result of specific expansion processes that give different cell types or in injuries resulting from diseases. They are not found in the embryonic stem cells, which are capable of differentiating into all types of cells in the body. Adult stem cells were initially isolated from bone marrow (BM) (Marrow Bone), then other locations of adult stem cells were identified (liver, pancreas, intestine, heart, dermis, dental pulp, cornea, brain, spinal cord). These cells

had many important applications in the field of tissue engineering, used as a model to identify the molecular mechanisms causing genetic diseases, study the effect of drugs and medications, repair nerve tissue damage, and cellular therapy. Among the most important applications of adult stem cells is the treatment of malignant blood diseases, which depends on the transplantation of healthy bone marrow from a donor, provided that there is tissue compatibility between the donor and the donor (Budday, 2015).

Stem cells are found in umbilical cord blood: The placenta and umbilical cord form the link between a pregnant mother and her fetus throughout pregnancy, where nutritional exchange takes place. Umbilical cord blood is the blood trapped within the vessels of the placenta and umbilical cord, which are amputated immediately after birth. Umbilical cord blood samples are collected within the first 20 minutes of birth and stored under suitable freezing conditions for clinical and research purposes, due to their potential to contain various types of pluripotent stem cells, including hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), and vascular endothelial cells. Many other cell types that have not yet been precisely characterized have also been found in umbilical cord blood (Chin, 2014).

Stem cells found in amniotic fluid: Amniotic fluid is the watery medium that surrounds the fetus and allows it to float flexibly during pregnancy. It plays a role in protecting the fetus from external shocks and facilitating its exit during birth.A 2007 study by Atala and colleagues at Harvard University revealed that this fluid contains pluripotent stem cells similar to embryonic stem cells, derived from fetal tissue. Studies have proven this. It is worth noting that these cells can be directed to differentiate into various cell types (Atala 2012, Abdulrazzak et al., 2013). They do not form teratoma tumors during culture in vitro or in vivo, and they do not face any of the difficulties or ethical problems in research and treatment fields. Therefore, they have a desirable and more preferred position among researchers compared to embryonic stem cells as a promising tool that can be preserved and frozen in suitable conditions for the purpose of diagnosing and treating many diseases (Rodrigues et al., 2012).

2- Hematopoietic Stem Cells:

2-1. Hematopoiesis and the Origin of Hematopoietic Stem Cells:

Hematopoiesis is a process by which blood cells are continuously replaced from at least eight cell series or lineages, starting from a single cell population, the pluripotent hematopoietic stem cell, throughout a person's life. These stem cells are rare, comprising 0.001% of all nucleated bone marrow cells. These are normally dormant cells, remaining in the Go or G phase of the cellular cycle. Embryological studies have indicated that hematopoiesis begins in the yolk sac approximately 7 days after embryonic development. After the 10th day, the liver becomes the primary site for hematopoietic cell formation. After 6 months, the bone marrow becomes the primary site for hematopoietic cell formation and continues to do so throughout the individual's life (Clapp et al., 1989). However, more recent studies in mammalian embryos, particularly mice, have indicated that CD34 hematopoietic stem cells form near the ventral wall of the aorta after 5 weeks of gestation. These studies have suggested that these stem cells originate in the gonadal region (AGM), the progenitor cells of the aorta (Sugiyama and Sasaki, 2013), and the marrow, and maintain hematopoietic cell production throughout the individual's life. When these cells are transplanted In adult animals, the ability to generate

blood cells of various lineages is limited. On the other hand, the process of blood cell formation involves progressive restriction of development, with an increase in the ability to proliferate and a decline in the self-renewal capacity of progenitor cells. After specialization, these cells become less or incapable of proliferating, and their lifespan is also shortened (Konuma et al., 2011).This maturation and differentiation process is tightly controlled, and any disruption in it leads to leukemia, anemia, immunodeficiency, or the absence of certain cell types (cytokine deficiency) and the resulting abnormalities (Peault and Tavian, 2003).

Hematopoiesis begins when CD34-CD45 pluripotent stem cells give rise to CD34-CD45 myeloid progenitor cells and lymphoid progenitor cells. Colonies of these cells can be detected in the spleens of mice irradiated with lethal doses eight days after injection using the Spleen Colony Assay. Therefore, these cells are called colony-forming units (CFUs). They are characterized by a limited capacity for self-renewal and the ability to form blood cells of various types when cultured in liquid or semisolid media (SCF, EPO, IL, G-CSF, M-CSF, GM-CSF, IL-3). These cells contain hematopoietic growth factors such as IL-6-C-Kit-ligand, IL-11, and others, which direct the differentiation of colony-forming cells into specialized mature blood cells (Zhang et al., 2010).It is worth noting that the process of hematopoietic cell formation is a conserved process regulated by complex molecular mechanisms that have been and continue to be the subject of ongoing research. A number of essential genes responsible for the formation of hematopoietic stem cells and the function of these cells in adults have been identified (Colpitts et al., 2013).The effect of hematopoietic growth factors, which are linked to Specific receptors on cell surfaces generate complex and intertwined cascades of signaling events within the cell, resulting in changes in gene expression that direct the cell toward proliferation or differentiation. Hematopoietic cells respond to growth factor signals by activating their receptors, which possess tyrosine kinase activity or are bound within the cell to proteins with tyrosine kinase activity, such as C-kit. Mutations in this receptor cause macrocytic anemia, impaired splenic colonization, and long-term failure of hematopoiesis. Mutations in this receptor's ligand also lead to the formation of a nurturing environment or niche that does not support stem cell growth (Saran et al., 2013).Among the most important receptors involved in hematopoiesis are cytokine receptors, which transmit signals through the Jak/Stat and Mak1/Erk pathways. Hematopoietic cytokines play a fundamental role in maintaining the steady state of healthy hematopoiesis. For example, the erythropoietin (Epo) receptor plays a role in the proliferation and survival of red blood cell-producing cells and in directing the differentiation of their progeny into red blood cells. Mutations in this receptor lead to the death of mice on day 13, or to impaired hematopoietic formation in fetal livers (Todaro et al., 2013).

On the other hand, genetic analysis has revealed a key role for several transcription factors in the formation of hematopoietic precursors. Some of these factors have a general effect in regulating the expression of specific genes that are specific to the differentiation and maturation of hematopoietic cells, while others are specific to differentiation into specific cell types. Evidence suggests that mutations in these cells affect the differentiation and maturation of all blood cell lineages, while others are specific to a specific lineage. For example, mutations in the GATA factor halt the differentiation and maturation of all blood cells, while mutations in factors 1, Rbtn2, and Pu halt the maturation of only red blood cells (Orkin, 1995).

2-2. Hematopoietic Stem Cell Transplantation:

The traditional source of hematopoietic stem cells has traditionally been bone marrow. Bone marrow was transplanted to enable doctors to increase the intensity of chemotherapy and radiation therapy doses and to eliminate endogenous cancer cells. It has therefore been used to treat lymphomas, leukemias, multiple myeloma, and breast cancer.

The procedure is performed either by lumbar puncture or by inducing the transfer of hematopoietic stem cells from the bone marrow to the peripheral blood, which are then collected for transplantation (Dasgupta et al., 1996). Bone marrow transplants have long been used in both genetic engineering and cell therapy (Vose, 2013). Cells prepared in this manner have played an important role, particularly in treating blood disorders and abnormalities such as thalassemia, thrombocytopenia, leukemia, sickle cell anemia, leukemia, immunodeficiency, and other leukemic bone marrow abnormalities (Daley, 2012).One of the advantages of treatment using hematopoietic stem cells isolated from bone marrow is that there is no need to understand the details of the process as a condition for implementing the treatment. The number and fate of the transplanted cells are regulated, and the risk is minimal. Toxicity from this treatment is limited to the acute phase during the preparation of the host to accept the graft, and treatment is administered only once. In contrast, chemotherapy, which uses chemicals that act on endogenous molecular targets, typically has cytotoxic effects wherever these target molecules are expressed. These chemotherapy treatments are, by their nature, chronic and persistent as long as the disease persists (Weissman, 2000).However, bone marrow transplantation has encountered challenges, requiring significant pre-transplant laboratory work for both the host and donor. After obtaining the donor's consent and informing them of the risks and nature of the procedure, the donor is prepared in the laboratory, including a medical history, chest x-rays, electrocardiograms, blood cell counts, clotting factor testing, and infectious marker testing. General anesthesia and hospitalization are required for the transplant. The isolation process may sometimes cause symptoms or harm to the donor or patient (206%), including pain at the collection site, fatigue, pain while walking or sitting, and rare conditions (0.1-0.3%) that may threaten the donor's social and professional life, such as mechanical bone damage, iliac hernia, or sciatica. In addition, the withdrawal of these cells may be accompanied by infections and bleeding. Immune rejection resulting from tissue incompatibility, which requires continuous treatment with immunosuppressive drugs, and sometimes viral infection, are among the main reasons for searching for an alternative to bone marrow cells.

In the last decade, peripheral blood has become a more popular source than bone marrow as an alternative, proven to be less morbid and less lethal, and the replacement of damaged blood cells is faster. However, studies have shown that there is an increase in cases of graft-versus-host disease (GVHD) associated with an increase in the number of T lymphocytes and natural killer cells in the recipient patient, which come from the donor (Bojanic et al., 2009). This has prompted researchers since 1970 to study hematopoietic stem cells isolated from umbilical cord blood (Koestenbauer et al., 2009), which fall under the category of multipotent adult stem cells, as they have more restricted functional properties compared to embryonic stem cells, in addition to their ability to self-dividing and continuous.

2-2-3. Characteristics of hematopoietic stem cells in umbilical cord blood:

The presence of stem cells in umbilical cord blood is believed to be related to growth factors released by placental cells or to low oxygen tension at birth. This is evidenced by the fact that the numbers of these stem cells in the newborn's blood decrease significantly within hours of birth, falling within the normal range observed in adults (Roy et al., 2012). Furthermore, the absolute number and percentage of CD34 hematopoietic stem cells (HSCs) among the total monocytes (MNCs) are inversely proportional to gestational age. Attempts to use umbilical cord blood (UCB), in particular, as a source of hematopoietic stem cells date back to the late 1960s and early 1970s. The first report by the Ende brothers of an attempt to transfuse umbilical cord blood into a patient with chemotherapy-treated leukemia was published in 1972. Later, two separate studies demonstrated that (Koike K, 1983 and Vidal JB, 1985) demonstrated that umbilical cord blood contains hematopoietic stem cells in sufficient numbers to perform bone marrow transplantation, and that storing these cells under cryopreserved conditions does not affect their viability or proliferative capacity. Broxmeyer and colleagues conducted a series of studies investigating the hematopoietic stem cell content of umbilical cord blood and the characteristics of these cells. They also developed successful methods for collecting and storing cord blood for medical use. These efforts led to the first successful cord blood cell transplantation The umbilical cord blood was transplanted into a child suffering from Fanconi anemia on October 6, 1988. The long-term success of the transplant and the differentiation of the transplanted cells into myeloid and lymphoid lineages confirmed the presence of pluripotent stem cells in umbilical cord blood (Broxmeyer et al., 1992).Broxmeyer and colleagues also evaluated the use of cord blood cells in adult therapy. Although the numbers of nucleated cells are much lower than those contained in bone marrow transplants, these cells generated in cord blood had a greater capacity for multiplication and clonal expansion in short-term liquid cultures. This was confirmed by the findings of Cardoso (Broxmeyer et al., 1992; Cardoso et al., 1993), found that CD34+CD38 cells multiplied 6-7 times more than cells isolated from bone marrow. Several studies have indicated that Studies suggest that this may be due to the fact that the telomeres of hematopoietic stem cells (HSCs) isolated from umbilical cord blood (UCB) are longer than those of cells in bone marrow (BM), making them able to survive longer in culture media (Zimmermann et al., 2004, Schuller et al., 2007).Based on the success of cord blood transplants, the International Cord Blood Transplant Registry (ICBTR) was established in 1992. The first cord blood bank (ICBTR) was established in 1993 at the New York Blood Bank to store and preserve cord blood units. The European Cord Blood Transplant Registry (ECTR) was also established. By 2003, more than 100,000 histologically typed cord blood units had been stored and ready for transplantation, benefiting 3,500 patients, mostly children (Eapen et al., 2010). This has encouraged other countries and private institutions to establish cord blood banks, including Arab countries.

The stem cells found in cord blood are similar to those found in bone marrow in terms of their ability to self-renew and differentiate into different cell lines. However, studies indicate that these cells are primitive cells, although they express the CD34 and CD33 antigens and HLA-Dr. This differs from stem cells found in the bone marrow, which express these antigens when differentiated (Traycoff et al., 1994).

The researchers demonstrated that the CD38 antigen distinguishes between different populations of these stem cells. While CD34CD38 cells represent a dormant population, CD34CD38 cells represent stem cells with a long-term clonogenic capacity in the culture medium for more than 8 weeks. This capacity accelerates the response of these cells to cytokine stimulation in the culture medium. Each CD34 cell generates a larger number of cells compared to its counterparts in the bone marrow. When Lansdorp compared the proliferation of stem cells isolated from umbilical cords with those isolated from bone marrow or fetal liver in a serum-free medium supplemented with a mixture of cytokines, specifically EPO, SCF, and IL-6, he found that the number of CD34 cells isolated from bone marrow remained constant, while the number of CD34 cells isolated from cord blood increased hundreds offold and the number of CD34 cells isolated from fetal liver increased thousands offold (Lansdorp et al., 1993).Carow also demonstrated that hematopoietic cells present in cord blood have a greater capacity to proliferate in culture dishes compared to hematopoietic cells isolated from bone marrow. When cord blood plasma was added to the culture medium, this capacity to proliferate was significantly enhanced, indicating the presence of other growth factors in cord plasma not found in adult blood (Carow et al., 1993). Lewis demonstrated that umbilical cord blood has an advantage over marrow in that it contains higher numbers of myeloid and lymphoid progenitor cells at day 0 and after 5 weeks of culture (Lewis and Verfaillies, 2000).In in vivo studies, this number was estimated at one CD34CD38 stem cell out of 44 cells, using a technique of direct injection into the bone marrow of immunodeficient mice (Yahata et al., 2003) instead of injection via the tail vein.A study demonstrated that umbilical cord blood contains CD34 progenitor cells capable of forming blood cells in immunodeficient mice, in addition to their ability to On reproduction, especially since the percentage of generating cells in case of division in the blood of the umbilical cord reaches 50%

Conclusion:

Stem cell therapy advancements have pushed us closer to realizing regenerative medicine's full potential. This science has made great development, from pluripotent stem cell production to gene editing and clinical applications, and regulatory frameworks are being built to ensure the safety and efficacy of stem cell therapies. Overall, stem cell therapy represents a very bright future for customized medicine, creative uses, and innovative procedures that have the potential to change healthcare. The use of stem cell therapy has the potential to revolutionize disease and injury treatment, giving hope to a significant number of patients all over the world. More revolutionary discoveries and novel strategies to improve human health and well-being should be expected as research in this area advances.

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