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Potency of Various Types of Stem Cells and their Transplantation

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Abstract

Stem cells are stirring great excitement in medical research. Stem cells are characterized by their three special properties of self renewal, differentiation and unspecialized nature. The capacity to differentiate into specialized cell types and be able to give rise to any mature cell type is referred to as potency. Human stem cell research holds an enormous potential and contribute to the understanding of fundamental human biology. Stem cell therapy is an amazing modern medical advancement that goes straight to the source of the problem and treats various disorders. Stem cell therapies are playing a major role in cell transplantation biology. This review describes various types of stem cells, their potency and transplantation.

Keywords: Stem Cells; Totipotent; Pluripotent; Multipotent; Oligopotent; Unipotent; Embryonic Stem Cells; Fetal Stem Cells; Cord Blood Stem Cells; Adult Stem Cells; Induced Pluripotent Stem Cells; Autologous Stem Cell Transplantation; Haematopoietic Stem Cell Transplantation; Mesenchymal Stem Cell Transplantation; Allogeneic Stem Cell Transplantation; Syngeneic Stem Cell Transplantation

Abbreviations: SC: Stem Cell; ESC: Embryonic Stem Cells; hESC: Human Embryonic Stem Cells; UCBT: Umbilical cord blood transplantation; BMSCs: Bone Marrow Stem Cells; HSCs: Hematopoietic Stem Cells; MSCs: Mesenchymal Stem Cells; iPSC: Induced pluripotent Stem Cells; HSPCs: Hematopoietic Stem and Progenitor Cells; ALC-15: Day 15 Absolute Lymphocyte Count; APHSCT: Autologous Peripheral Hematopoietic Stem Cell Transplantation

Introduction

Stem cells (SC) are biological cells found in almost all multicellular organisms that can divide and differentiate into diverse specialized cell types and can self-renew to produce more stem cells. Stem cells have the remarkable potential to develop into many different cell types in the body during early life and growth. In many tissues they serve as a sort of internal repair system, dividing essentially without limit to replenish other cells. When a stem cell divides, each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function, such as a muscle cell, a red blood cell, or a brain cell. Stem cells have also long-term self-renewal ability and capacity to give rise to one or more types of differentiated progeny [1]. Recent advances in stem cell technology have been a key to treatment of patients [2]. The ideal scientific outcome is to eradicate cancer at the level of stem cells [3].

Stem cells are characterized by their three special properties of self renewal, unspecialized nature and differentiation [4]. Stem cells are capable of dividing and renewing themselves for long periods. Stem cells may replicate many times, or proliferate. Stem cells are unspecialized in that they do not have any tissue-specific structures that allow it to perform specialized functions. However, unspecialized stem cells can give rise to specialized cells, including heart muscle cells, blood cells, or nerve cells. When unspecialized stem cells give rise to specialized cells, the process is called differentiation. While differentiating, the cell usually goes through several stages, becoming more specialized at each step. Asymmetric division is the process by which stem cells divide to generate the diversity of cell types that populate adult organisms. Asymmetric division has been found in virtually all developing systems where stem cells need to simultaneously proliferate and generate differentiated cells [5]. In most tissues, stem cells are rare. As a result, stem cells must be identified prospectively & purified carefully in order to study their properties [6]. Human stem cell research holds an enormous potential to contribute the understanding of fundamental human biology [7]. Because of their ability stem cells can differentiate into any tissue type, they have huge potential in various disease therapies and traumatic injuries [8].

Stem cell research contributed to gain a fundamental understanding of how organisms grow and develop and how tissues are maintained throughout adult life [9]. Human keratinocytes are needed for tissue engineering of skin applied in tissue repair and regeneration aimed at clinical application [10]. Given the recent interest in the potential use of embryonic and adult stem cells for basic and applied research, including testing the origin of human cancer, attempts have been made to characterize markers that would identify these stem cells [11]. The promise of stem cell-based therapy for advancement of research in regenerative medicine has stimulated a great number of clinical trials, particularly for previously untreatable diseases [12]. Stem cell transplantation through cell replacement or as vector for gene delivery [6] is a potential strategy for the treatment of neurodegenerative diseases including Alzheimer's disease [13], Parkinson's disease [14], Huntington's chorea, HIV-associated dementia, multiple sclerosis [15], amyotrophic lateral sclerosis, and glaucoma [16] caused by different mechanisms [17]. Bone marrow derived pluripotent stem cells hold a great promise for therapeutic repair of injured central nervous system [18].

Stem cells are multipotent, self-renewing and clonigenic cells that can replace apoptotic [19], dysfunctional and/or senescent cardiomyocytes, fibroblasts and endothelial cells by translineage

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commitment or cell fusion [20]. Stem cell therapy holds a great promise for the repair of injured tissues and organs. Stem cells are undifferentiated cells that undergo both self-renewal and differentiation into one or more cell types, & are found in adult and embryonic tissues and have potential uses in therapies designed to repair and regenerate organs [21]. Recently, human adult stem cells have been developed as important tools for several cell-based therapies, some of which include tissue engineering approaches [22]. The field of stem cell biology is rapidly integrating with the aid of clinical trials. Stem cell trafficking is orientated and directed movement of cells toward a specific stimuli [23]. Adult stem and progenitor cells have shown reparative potential in pre-clinical models of ischemia and infarction [24]. Stem cell therapy is an amazing modern medical advancement that goes straight to the source of the problem and treats various disorders [25].

Potency of Stem Cells

The capacity to differentiate into specialized cell types and be able to give rise to any mature cell type is referred to as potency. Potency of the stem cell specifies the differentiation potential i.e., the potential to differentiate into different cell types.

- *Totipotent* stem cells can differentiate into embryonic and extraembryonic cell types. Such cells can construct a complete, viable organism. These cells are produced from the fusion of an egg and sperm cell. The only totipotent cells are the fertilized egg and the cells produced by the first few divisions of the fertilized egg are also totipotent. Totipotent stem cells give rise to somatic stem/progenitor cells and primitive germ- line stem cells [26].
- *Pluripotent* stem cells are the descendants of totipotent cells and can differentiate into nearly all cells, i.e. cells derived from any of the three germ layers. These pluripotent cells are characterized by self-renewal and a differentiation potential for all cell types of the adult organism [27]. These are true stem cells, with the potential to make any differentiated cell in the body. Embryonic Stem Cells come under this category. Human pluripotent stem cells would be invaluable for *in vitro* studies of aspects of human embryogenesis [28].
- *Multipotent* stem cells can differentiate into a number of cells, but only those of a closely related family of cells. These are true stem cells but can only differentiate into a limited number of types. For example, the bone marrow contains multipotent stem cells that give rise to all the cells of the blood but not to other types of cells. Adult Haematopoeitic Stem Cells are multipotent. Adipose tissue is a source of multipotent stem cells [29]. Multipotent stem cells form multiple blood cell lineages [30].
- *Oligopotent* stem cells can differentiate into only a few cells, such as lymphoid or myeloid stem cells. The corneal epithelium is a squamous epithelium [31] that is constantly renewing and is Oligopotent [32].
- *Unipotent* cells can produce only one cell type, their own, but have the property of self-renewal, which distinguishes them from non-stem cells. Such Unipotent cells include muscle stem cells. Most epithelial tissues self-renew throughout adult life due to the presence of unipotent progenitor cells [33].

Types of Stem Cells

Embryonic Stem Cells (ESC)

Embryonic stem cells have the ability to form any fully differentiated cell of the body [34]. During the early stages of embryonic development the cells remain relatively undifferentiated and possess the ability to become, or differentiate, into almost any tissue within the body. Cells in the early embryonic stage are totipotent and can differentiate to become any type of body cell. After about seven days, the zygote forms blastocyst, which contains a mass of cells that eventually become the fetus, as well as trophoblastic tissue that eventually, becomes the placenta. Embryonic stem cells (ESCs) derived from the early embryos possess two important characteristics: self-renewal and pluripotency [35]. The cells from the blastocyst are pluripotent and the cells at this stage are referred to as blastocyst embryonic stem cells. ES cell lines are sometimes referred to as immortal due to their ability to keep dividing (self-renewing) over many generations. Human embryonic stem cells could be used to seek out and destroy a fatal form of brain cancer. ES cells may have great potential in forming the basis of long-term therapies, but issues regarding their safety must be overcome first. Human embryonic stem cell (hESC) research occupies an exceptional place in science [36]. ESCs also provide opportunities for the development of large quantities of therapeutically useful cells [37]. Derivation of human pluripotent embryonic stem cell lines and recent advances in hESC biology has generated great interest in the field of stem cell-based engineering [38]. Human embryonic stem cells open new avenues for autologous cell-based therapy in degenerative diseases, bypassing the ethical and immunological problems [39]. Embryonic stem cells have huge potential in the field of tissue engineering and regenerative medicine [40].

Fetal Stem Cells

Fetal stem cells are primitive cell types found in the organs of fetus. Fetal stem cells can be isolated from fetal blood and bone marrow as well as from other fetal tissues, including liver and kidney [41]. As their name suggests, fetal stem cells are taken from the fetus. The developing baby is referred to as a fetus from approximately 10 weeks of gestation. Most tissues in a fetus contain stem cells that are pluripotent and drive the rapid growth and development of the organs. Fetal blood is a rich source of haemopoietic stem cells, which proliferate more rapidly than those in cord blood or adult bone marrow [42]. Like adult stem cells, fetal stem cells are generally tissue-specific, and generate the mature cell types within the particular tissue or organ in which they are found. The classification of fetal stem cells remains unclear and this type of stem cell is currently grouped into an adult stem cell.

Cord Blood Stem Cells

Blood from the umbilical cord contains some stem cells that are genetically identical to the newborn. They are multipotent stem cells [43] that are able to differentiate into certain, but not all, cell types. At birth the blood in the umbilical cord is rich in blood-forming stem cells. The applications of cord blood are similar to those of adult bone marrow and are currently used to treat diseases and conditions of the blood or to restore the blood system after treatment for specific cancers. Like the stem cells in adult bone marrow, cord blood stem cells are tissue-specific. Blood can be collected from the umbilical cord of a newborn baby shortly after birth. This blood is rich in cord blood stem cells that can be used to generate blood cells and cells of the immune system. Blood stem cells can be used to treat a range of blood

disorders and immune system conditions such as leukaemia and sickle cell anaemia. The umbilical cord blood is often banked, or stored, for possible future use of stem cell therapy. As this blood originated from the person receiving it, there would be no problem with rejection of the transplanted tissue. Alternatively, the cord blood may be donated to other people in need of a transplant. The discovery that stem cells can be obtained from umbilical cord blood instead of the more controversial source of embryonic SC's, has renewed interest on the new, exciting therapeutic potentials of this technology [44]. Umbilical cord blood transplantation (UCBT) is increasingly used for a variety of malignant and benign hematological and other diseases [45].

Adult Stem Cells

Adult stem cells have been isolated from several tissue sources, including the central nervous system, bone marrow, retina and skeletal muscle [46]. Adult stem cell refers to any cell which is found in a developed organism that has two properties that is the ability to divide and create another cell like itself and also divide and create a cell more differentiated than itself. Also known as somatic stem cells and germline stem cells giving rise to gametes. They are found both in children, as well as adults. Pluripotent adult stem cells are rare and generally small in number but can be found in a number of tissues including umbilical cord blood. Most adult stem cells are lineage-restricted i.e., multipotent and are generally referred to by their tissue origin. These include mesenchymal stem cell, adipose-derived stem cell, endothelial stem cell, dental pulp stem cell, etc. Adult stem cell treatments have been successfully used for many years to treat leukemia and related bone/blood cancers through bone marrow transplants. Adult stem cells are also used in veterinary medicine to treat tendon and ligament injuries in horses. An extremely rich source for adult mesenchymal stem cells is the developing tooth bud of the mandibular third molar. The adult stem cells undergo rapid proliferation when it needs to regenerate the specialized tissues [47].

Development of a multicellular organism is accomplished through a series of events that are preprogrammed in the genome [48]. Adult or somatic stem cells exist throughout the body after embryonic development and are found inside of different types of tissue. These stem cells have been found in tissues such as the brain, bone marrow, blood, blood vessels, skeletal muscles, skin, and the liver. They remain in a quiescent or non-dividing state for years until activated by disease or tissue injury. Adult stem cells can divide or self-renew indefinitely, enabling them to generate a range of cell types from the originating organ or even regenerates the entire original organ. It is generally thought that adult stem cells are limited in their ability to differentiate based on their tissue of origin, but there is some evidence to suggest that they can differentiate to become other cell types. Adult stems cells, including Bone Marrow Stem Cells (BMSCs); exhibit a certain degree of developmental plasticity that enables them to differentiate across boundaries of lineage, tissue and germ layers [49]. The use of adult stem cells isolated from patients could solve immunological problems associated to cell transplant [50]. Adult bone marrow [51] contains at least two types of stem cells: hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs) [52].

Induced Pluripotent Stem Cells

Induced pluripotent Stem cells (iPSC) are created by inducing the specialized cells to express genes that are normally present in embryonic stem cells and that control cell functions. Embryonic stem cells and iPS cells share many characteristics, including the ability become the cells of all organs and tissues, but they are not identical. IPS cells are a powerful method for creating patient- and disease-specific cell lines for research. These are not adult stem cells, but rather reprogrammed cells with pluripotent capabilities. Using genetic reprogramming with protein transcription factors, pluripotent stem cells equivalent to embryonic stem cells have been derived from human adult skin tissue. Frozen blood samples can be used as a source of induced pluripotent stem cells, opening a new avenue for obtaining the valued cells. iPSCs are useful tools for drug development and modeling of diseases, and scientists hope to use them in transplantation medicine. iPSCs are derived from somatic cells, epigenetically reprogrammed to lose tissue-specific features and gain pluripotency. Similar to hESCs, they can theoretically differentiate into any type of cells [53]. The concept of induced pluripotent stem cells remains an important area of focus for future research and has serious implications for the stem cell cancer theory [54]. The creation of pluripotent stem cells from adult cells by the introduction of reprogramming transcription factors, called induced pluripotent stem cells allowed the derivation of patient-specific pluripotent stem cells without the need of creation of a human blastocyst after cloning by somatic cells nuclear transfer [55]. Induced pluripotent human cell lines are useful in the production of new disease models and in drug development as well as in transplantation medicine [56].

Transplantation

Stem cells received much attention for their potential use in cell-based therapies for various human diseases [57]. Stem cell therapies play a major role in cell transplantation biology [13]. There are 3 basic types of transplants. They are called autologous, allogeneic, and syngeneic. The type of transplant depends on where the stem cells come from.

Autologous stem cell transplant

In this type of transplant the patient's own stem cells are taken before cancer treatment. The stem cells are removed or harvested, from either bone marrow or blood and then frozen. After high doses of chemo or radiation therapy the stem cells are thawed and given back to the patient. The advantages of autologous stem cell transplant are that the patients get back their own cells and there would be no risk of transplant rejection. This kind of transplant is mainly used to treat some leukemias and lymphomas, and multiple myeloma. It is sometimes used for other cancers, especially in children. Adult Stem Cells include Haematopoietic Stem cells and Mesenchymal Stem Cells. Autologous Stem Cell Transplantation plays an important role in the treatment of follicular lymphoma [58]. Autologous platelet rich plasma is used in the treatment of tissue defects [59].

Haematopoietic Stem Cell Transplantation: Hematopoietic stem cells (HSCs) are the most routinely transplanted adult stem cell. Currently, they are utilized for the treatment of several genetic and acquired diseases including blood cancers, autoimmune disorders, and hematopoietic defects. High-dose immunosuppressive therapy with autologous hematopoietic stem cell transplantation shows promising results in the treatment of severe autoimmune diseases [60]. CXCR4 receptor axis plays crucial role in retention of hematopoietic stem and progenitor cells (HSPCs) in bone marrow [61]. Day 15 absolute lymphocyte count (ALC-15) ≥ 500 cells/μl has been reported to be a prognostic factor for survival post autologous peripheral hematopoietic stem cell transplantation (APHSCT) [62]. HCSs are ideal candidates for gene therapy applications because they possess the capacity for self replication and functionality to propagate the entire hematopoietic lineage [63].

Mesenchymal Stem Cell Transplantation: Mesenchymal stem cell [MSC] is the conventional term used to describe the collection of poorly defined multipotent mesenchymal stromal cells [64]. Mesenchymal Stem Cells are used for cell therapy for the treatment of various neurological disorders [65]. Mesenchymal stem cells are defined as self-renewable, multipotent progenitor cells with the ability to differentiate, under adequate stimuli, in several mesenchymal lineages [66]. MSCs are multipotent stem cells that can differentiate into a variety of cell types, including osteoblasts (bone cells), chondrocytes (cartilage cells) and adipocytes (fat cells) [67]. Mesenchymal stem cells can be isolated from embryonic or adult tissues such as bone marrow and adipose tissue [68]. Bone marrow-derived mesenchymal stem cells have the capacity to differentiate into several cell types. Bone marrow samples were collected from healthy donors after informed consent. MSCs were isolated via their plastic adherence [69]. Adult Mesenchymal stem cells (MSCs) provide another promising approach for cartilage regeneration [70]. Therapeutic cell populations, including bone marrow stem cells, have the potential to interact with ischemic tissues [71]. Mesenchymal progenitors are released from the bone marrow and are used in the treatment of bone disorders [72]. To examine the degree of proliferation of the mesenchymal stem cell, the number of CFU-F (colony-forming unit of fibroblast) is determined [73].

Allogeneic stem cell transplant

The stem cells do not come from the patient, but from a donor whose tissue type closely matches the patient. The donor is usually a family member. Blood taken from the placenta and umbilical cord of newborns is a newer source of stem cells for allogeneic transplant. The advantage of allogeneic stem cell transplant is that the donor stem cells make their own immune cells, which may help destroy any cancer cells that may remain after high-dose treatment; this is called the graft-versus-cancer effect. Another advantage is that the donor can often be asked to donate more stem cells or even white blood cells if needed. Stem cells from healthy donors are also free of cancer cells. Allogeneic transplant is most often used to treat certain types of leukemia, lymphomas, and other bone marrow disorders such as myelodysplasia. Allogeneic stem cell transplantation requires the harvest of an adequate number of stem cells from a histocompatible donor [74]. Allogeneic stem cell transplants have been performed for treatment of major diseases [75].

Syngeneic stem cell transplant

This is a special kind of allogeneic transplant that can only happen when the donor and recipient are identical twins or identical triplets who always have the same tissue type. An advantage of syngeneic stem cell transplant is that graft-versus-host disease will not be a problem.

Transplantation is also limited by mortality of the transplanted cells after transplantation by apoptosis or macrophage activity independent of the autologous or allogeneic procedures used [76]. Cytomegalovirus is one of the most prevalent infectious pathogen in transplant recipients, including those receiving bone marrow or stem cell grafts [77].

Conclusion

Stem cells received much attention for their potential use in cell-based therapies for various human diseases. Potency of the stem cell specifies the differentiation potential and is an important factor that is responsible for the distinguishing nature of the stem cells. Stem cells open new avenues for transplantation therapy. The use of autologous transplantation solves immunological problems associated to cell transplant. Allogeneic transplantation also plays an important role in transplantation biology. Thus by using various stem cell transplantation techniques, major complications can be resolved.

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