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Potential Applications of Different Types of Adult Stem Cells Toward Medical Interventions

Medical Science

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ABSTRACT

Stem cells are undifferentiated progenitor cells that are capable of self renewing and differentiating into specific cell lineages. Embryonic and adult stem cells are the two main types of stem cells. The pluripotent nature of embryonic stem cells distinguishes them from adult stem cells. Adult stem cells are multipotent and are able to differentiate into a limited number of cell types. Unlike embryonic stem cells, the use of adult stem cells is not controversial or unethical because they can be derived from adult tissue samples rather than from embryos. The self-renewal and multi-differentiative potential of adult stem cells makes them highly suitable for various clinical applications because they can be harvested directly from patients themselves. Some types of adult stem cells are capable of transdifferentiation, whereas the ability of others remains unknown. More studies should focus on revealing the molecular and cellular pathways involving these adult stem cells and improving the methods of harvesting and culturing adult stem cells up to the required number of cells. Some types of adult stem cells such as hematopoietic, cardiac, neural, adipose-derived, epidermal, hair follicle, and dental pulp stem cells, as well as their potential clinical applications, are reviewed in this paper.

Introduction

Stem cells are master cells that can develop and mature into up to 200 cell types in the human body. Specifically, stem cells are known to be undifferentiated, unspecialized progenitor cells that, under the response to particular signaling pathways, are capable of self-renewing and differentiating into specialized cells. The morphologies of stem cells are generally simpler compared with committed cells of the same lineages [1]. Depending on their origin and ability to differentiate, stem cells are termed differently as: umbilical cord stem cells, embryonic-derived stem cells, fetal stem cells and adult stem cells. In earlier years, umbilical cord blood was discarded as a waste material because the uses of blood stem cells were not known. The umbilical cord blood comprises hematopoietic stem cells (HSCs), which normally generate red blood cells and other immune cells. These umbilical cord stem cells are currently used to treat a wide range of blood disorders and autoimmune diseases [2]. Embryonic stem cells are derived from the inner mass of the blastocyst of the early embryo and can differentiate into any of the three primary germ layers (ectoderm, endoderm, mesoderm) of the embryo, as well as into germ cells [3-5]. Fetal stem cells are isolated from fetal blood, tissues, liver and kidney, as well as from the bone marrow [6]. Adult stem cells, also known as tissue-specific stem cells or somatic stem cells are undifferentiated cells that are found in fully differentiated and well-developed tissues. Because of their self-renewing and highly proliferative capacity over time, adult stem cells differentiate into mature cells of the tissues in which they reside. Although embryonic stem cells are pluripotent, they will develop into teratomas upon injection. Highly efficient and more selective methods are required to induce the proliferation and differentiation of embryonic stem cells. Additionally, various ethical debates revolve around the isolation and usage of embryonic stem cells [7]. As a result, more studies that are giving more promising outcomes for clinical applications have been conducted on adult stem cells. Because adult stem cells are capable of self-renewing due to their multipotent nature, these cells can potentially generate all cell types of each organ and are capable of successfully revitalizing the organ [8]. Self-renewal is the process of maintaining the number of cells in a population over a long period of time after the stem cells first divide. Multipotency is the ability of stem cells to generate daughter progenitor cells that can differentiate into specific cell types of that particular tissue or organ [9, 10]. There are many different types of adult stem cells, and all of them follow different cellular mechanisms for the processes of self renewal and differentiation [9]. The present review paper highlights the seven different types of adult stem cells and their applications toward medical interventions.

Hematopoietic stem cells

All blood cells develop from hematocytoblasts, which are pluripotent stem cells. They tend to replicate and differentiate very quickly to supply blood cells. Hematopoiesis is the process by which immature precursor cells develop into mature blood cells. The initial process of generating new blood cells begins during the very early stage of embryonic development and continues for the entire life span [11]. Billions of new blood cells produced in the body are derived from hematopoietic stem cells (HSCs). HSCs are categorized as either long or short term, as well as into multipotent progenitors, depending on the degree of their self-replenishing abilities. These HSCs are predominantly found in the bone marrow of adult mice and humans. They have the ability to differentiate into all of the mature blood cell lineages that are required for hematopoietic functioning, including macrophages, monocytes, neutrophils, basophils, eosinophils, erythrocytes, platelets, and dendritic cells, all of which are of the myeloid lineage, as well as T cells, B cells, and natural killer (NK) cells, all of which are of the lymphoid lineage [12-13]. To date,

HSCs are the best-characterized population of adult stem cells. These HSCs have been studied and investigated to develop treatments for hematological disorders such as non-malignant and malignant diseases. Allogeneic and autologous HSC transplantations are commonly referred to as HSCTs and are used for the treatment of leukemia, sickle cell anemia and various other hematopoietic disorders [14-16].

HSCT has long been practiced as a medical intervention for life-threatening primary disorders such as bone marrow failure syndromes, leukodystrophies, histiocytic disorders, severe autoimmune diseases and metabolic diseases, all of which fall under non-malignant diseases [17]. Usually, non-malignant diseases such as severe combined immune deficiencies (SCID) occur due to the dysfunctioning of T and B cells, resulting in immunocompromization. HSCT may help with the differentiation and proliferation of T and B cells, thereby replacing abnormal T and B cells with normal functioning cells [18]. It has also been reported that autoimmune diseases such as scleroderma, systemic lupus erythematosus (SLE), rheumatoid arthritis, refractory thrombocytopenia and pure red cell aplasia, multiple sclerosis, Sjogren syndrome, and inflammatory bowel disease have been effectively treated with autologous grafts of HSCs; these treatments resulted in increased engraftment rates, and the patients remained free of certain complications [19-21]. Replacing defective HSCs with the combination of HSCT and gene therapy was found to be the best curative option available for inherited blood diseases such as sickle cell anemia (SCA) or beta-thalassemia (β-thalassemia) [22, 23].

Malignant diseases occur in the cellular compartment of HSCs as a result of abnormal proliferation or due to the dysregulation of genetic factors [24]. Abnormal proliferation or malignancies of white blood cells, B cells and T cells result in non-Hodgkin lymphoma (NHL), which is treated by using both allogeneic and autologous HSCT [25, 26]. In the case of chronic lymphocyte leukemia, in which the abnormal or malignant B lymphocytes develop resistance to chemotherapy, allogeneic HSCT was found to be very effective [27, 28]. HSCT can also be combined with other chemotherapeutic agents to replace the loss of endogenous healthy stem cells by radiation, chemotherapy or other therapeutic regimens for the treatment of patients suffering from acute myeloid leukemia and lymphoma [29, 30]. Wilm's tumor, retinoblastoma, Ewing sarcoma of bone or germ cell tumors and ovarian cancers in children are treated with HSC therapy combined with chemotherapy, which is associated with a reduced risk of graft rejection and an increased survival rate [31-33].

Adult stem cells in cardiac repair

Heart-related diseases are the major cause of death worldwide. Stem cell-based therapies help to restore blood flow in the blood vessels via the differentiation of stem cells into multiple cardiac cell types, thereby improving cardiac function [34]. Adult cardiac stem cells (CSCs) are multipotent, self-renewing cells that give rise to cardiomyocytes and smooth muscle and endothelial cells. Adult CSCs are Lin-c-kit+ cells; when they are injected into an ischemic heart, they differentiate into vascular and endothelial smooth muscle cells, resulting in regeneration of the myocardium [35] . The c-kit+ CSCs are also able to differentiate into coronary vessels and cardiomyocytes. Notably, HSCs, bone marrow-derived mesenchymal stem cells, and umbilical cord blood stem cells are also capable of differentiating into all of the above mentioned cell types of the heart and are therapeutically used to treat chronic heart failure of both ischemic and non-ischemic origins [36, 37].

Studies have suggested that the myocyte renewal rate decreases over time in animals and humans [38, 39]. This is because myocyte apoptosis increases linearly with aging; as a result, approximately 95% of ventricular myocytes are lost [40]. The stem cell niche is the microenvironment where undifferentiated stem cells reside and wait for signals from supporting cells. Once they receive these signals, these stem cells divide and regenerate into specific cell types [41, 42]. The c-kit+ CSCs self-renew and differentiate into multicellular clones both in vitro and in vivo to give rise to differentiated progeny. In the cases of myocardial infarction (MI) and chronic aortic stenosis, the activation of c-kit+ CSCs occurs, resulting in self-renewal and differentiation into cardiomyocytes [43-45].

Different classes of bone barrow-derived cells, including HSCs, are being used to treat patients with acute and chronic ischemic cardiomyopathy. This is because these stem cells release cytokines that activate the endogenous progenitors that are responsible for tissue repair, thereby restoring ventricular function [46]. The c-kit+ HSCs resulted in remarkably increased levels of myocardial regeneration after MI [47-50]. The therapeutic efficiency of both HSCs and CSCs depends on the survival, proliferation, growth and differentiation of these stem cells within the myocardium of a damaged heart. HSCs have a greater growth potential than CSCs, but the transdifferentiation characteristic of HSCs may alter their growth behavior, and they may not reach the adult phenotype; therefore, CSCs are more suitable for cardiac repair [37].

Neural stem cells

Neural stem cells (NSCs) are found to be present in two main regions of the adult brain. These two populations are the NSCs that persist in the ventricular-subventricular zone (V-SVZ) and produce olfactory neurons and the NSCs that reside in the subgranular zone (SGZ) and give rise to neurons that are responsible for hippocampal formation and cognitive processes [51, 52]. These NSCs give rise to new neurons, which are known to be specialized populations of astrocytes that are responsible for interactions with the brain vasculature. Because the NSCs can self-renew, undergo mitosis, differentiate into neuronal and glial subtypes and migrate to injured sites, their potential to generate neurons is amplified and holds great therapeutic value for neurovascular and neurodegenerative diseases. The process involved in the generation of new neurons from NSCs and progenitor cells is known as neurogenesis. Altered and dysregulated neurogenesis in the hippocampal region results in temporal lobe epilepsy. Because neurogenesis in the SGZ is responsible for mood regulation, learning and memory, changes in neurogenesis cause various disorders such as Alzheimer's and Huntington's diseases [53-55]. Although most neurogenesis stops around birth, studies have clearly shown that new neurons are produced continuously by stem cells in the restricted regions of the adult mammalian brain throughout the lifespan. Also, the amount of neurogenesis that occurs in both the V-SVZ and SVZ zones decreases with aging [56, 57].

The V-SVZ niche: astrocyte NSCs in the V-SVZ zone come into contact with the ventricular lumen and blood vessels, thereby amplifying the number of progenitors. These progenitors differentiate into immature neurons, which migrate to the olfactory bulbs and mature into interneurons. The SGZ niche: astrocyte NSCs in the SGZ zone only come into contact with the blood vessels, giving rise to progenitors that differentiate into immature neurons. These immature neurons travel a short distance into the granule cell layer to integrate into the local circuitry, where they mature and become interneurons, which regulate SGZ NSCs.

By modulating the pathways involved in these niches that regulate NSCs, it could be possible to trigger astrocytes to differentiate into NSCs elsewhere in the brain. In cases of disease and injury, NSCs react sensitively to the pathologic conditions occurring in the adult brain, thereby changing the neurogenesis process. Increased NSC proliferation has been found after is-

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chemic stroke in the V-SVZ niche. After traumatic brain injuries, the proliferation of glial cells results in glial scars, which inhibit neurogenesis and complete wound healing. Glial cells and astrocytes also participate in classic neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington diseases and *Amyotrophic lateral sclerosis (*ALS)[58, 59]. Understanding the molecular mechanisms and the niche elements involved in the differentiation of NSCs in both the V-SVZ and SGZ zones may help to activate astrocytes elsewhere in the brain to induce neurogenesis and thereby replace lost neurons [51].

Adipose-derived stem cells

Adipose-derived stem cells (ASCs) are multipotent stem cells residing within the adipose tissue [60]. Adipose tissue comprises mature adipocytes, a stromal vascular fraction and ASCs. Almost all of the other adult stem cell types require ex vivo expansion or manipulation before they are clinically applied to ensure their efficacy and safety. Because of the ubiquitous nature of human adipose tissue, ASCs are easily obtained in larger populations with very little discomfort to the patients. Notably, ASCs differ in their characteristics depending on the location of the harvested adipose tissue. ASCs can be modulated by exposing them to different agents, thereby activating them to secrete various growth factors [61, 62]. Thus, when ASCs are transplanted into ischemic regions, they increase their secretion of growth factors required for wound healing and tissue repair. ASCs have the capability to differentiate into a variety of cell lineages with a greater proliferation rate both in vivo and in vitro [63]. For instance, ASCs of mesodermal origin can differentiate into ectoderm, endoderm and mesoderm.

ASCs are more efficient at promoting wound healing and tissue regeneration. It has been speculated that the healing efficacy of ASCs is due to the release of various growth factors, angiogenesis and the induction of fibroblast and keratinocyte proliferation [64]. In a clinical study, when tissue damaged by radiation was treated with ASCs, a significant improvement in new vessel formation was reported [65, 66]. In patients suffering from Crohn's and non-Crohn's diseases, complex fistulas were rapidly healed by the direct injection of ASCs along with fibrin glue sealant [67, 68]. The immunomodulatory effects of ASCs help to treat autoimmune diseases, allergic reactions and graft versus host disease (GVHD)[69].

ASCs can be induced to differentiate into adipogenic cell lineage to generate adipose tissues, which are of great demand for reconstructive and cosmetic surgery. Thus, the use of ASCs in fat grafting is mainly aimed to fix deformities and to conduct breast augmentation; ASCs are also used to treat chest wall radiation necrosis and to produce larger constructs for mastectomy reconstruction and other congenital defects [65, 70, 71]. Studies of the osteogenic differentiation of ASCs in murine models showed promising outcomes of ASCs in bone formation [72, 73]. Osteoarthritis (OA) is a more common form of joint disease, and there is considerable hope that ASCs could generate cartilage for treating degenerative joints via inducing the chondrogenic differentiation of ASCs. However, the clinical applications of both osteogenic- and chondrogenic-differentiated ASCs are greatly challenged in terms of time and cost for 3D bone and cartilage generation; thus, cartilage reconstruction by ASCs has not been demonstrated [71].

Another remarkable breakthrough regarding ASCs is their potential to differentiate into cardiomyocytes and endothelial and neuronal-like cells [74]. ASCs grown as monolayer sheets were found to be more efficient for myocardial repair. The engraftment of ASCs on scarred myocardium in rats reduced scarring and enhanced and replaced cardiac structure and function. These ASC sheets proliferate and form a thick layer over the infarcted muscle, forming new vessels and cardiomyocytes [75]. Thus, ASCs are capable of reducing the damage caused by myocardial infarction and increasing vascularization by secreting angiogenic and anti-apoptotic growth factors. Thus, ASCs enhance heart function and reverse remodeling in ischemically injured hearts [76].

Epidermal stem cells

Stem cells that are present in the epidermis and hair follicles help to maintain adult skin homeostasis and hair regeneration and also play an important role in repairing the epidermis after injuries. Epidermal stem cells that precisely reside in the bulge region of the hair follicle are called as hair follicle stem cells (HFSCs) [77-79]. These stem cells can regenerate the hair bulb under physiological conditions. Additionally, upon tissue injury, they can also regenerate the epidermis and sebaceous glands [80, 81]. It has been shown that patients with inherited structural and enzymatic skin defects such as Epidermolysis Bullosa could be treated using gene therapy in which the genes were modified and engineered to have functional autologous HFSCs, which are then transplanted to restore the damaged tissue [82]. Additionally, by targeting and manipulating the genes responsible for hair regeneration, unwanted hair could be permanently removed [81].

Apart from that, it has been revealed that the autologous hair follicle unit transplantation (FUT) method helps to regenerate ectopic hair follicles [83]. Toyoshima *et al.* reported that the regeneration of orthotopic hair has been performed via the intracutaneous transplantation of engineered hair follicle germ cells. The study further suggested that bioengineered hair follicles formed perfect hair structures by interacting with the surrounding host tissues, which include the epidermis, nerve fibers and arrector pili muscle [84].

Because of their multiple differentiation and proliferation abilities, hair follicle stem cells are also used in tissue engineering for skin reconstruction for wounds, trauma, deep burns and other skin-related disorders. These tissue-engineered skin substitutes were developed to overcome the limitations of autografts and allografts, including scarring, pain, infection and donor site morbidity in afflicted patients [85].

Dermal skin stem cells (mesenchymal hair follicle stem cells)

Multipotent stem cell progenitors derived from skin and discovered in the dermis are termed as skin-derived precursors (SKPs). These dermal skin stem cells can be maintained in culture for long periods of time and are able to differentiate into neurons, glia, and smooth muscle cells, including cells with peripheral neuron and Schwann cell phenotypes [86, 87]. SKP cells are also capable of differentiating into osteogenic, chondrogenic, adipogenic and neuronal precursor lineages. These characteristics make SKPs a better alternative for tissue regeneration repair than bone-marrow mesenchymal stem cells [88].

This interesting feature of SKP cells makes these adult-derived stem cells an accessible source of candidate cells for autologous cell-replacement therapy. A study by Kawase et al. revealed that SKP cells transplanted into the spinal cord after traumatic injury migrated to the wound area and differentiated into glial and neuronal cells [89]. Additionally, SKP cells play a role in replacing dermal cells during dermal repair [90]. A study by Reynolds and colleagues demonstrated the inductive ability of the dermal portion of the follicle. Follicle dermal sheath cells that were transplanted from one person to another generated follicles that grew into hair without undergoing the rejection process normally associated with allografts [91]. Although there are no diverse applications of human dermal stem cells, more studies have been conducted on animals to discover other applications

of SKP cells. As an example, McKenzie and co-workers used the skin as a source of neural crest precursors to treat the injured and dysmyelinated nervous system [92]. Additionally, a study reported by Lako et al. showed that SKP cells of murine adult hair follicle cells could produce hematopoietic colonies in vitro and contribute to all blood lineages in vivo. The data from this study revealed that SKP cells have an intriguing hematopoietic potential [93]. Furthermore, the differentiation of SKP cells into adipocyte/osteocyte phenotypes was also reported [94]. This has been proven to be important for tissue engineering applications.

Human dental pulp stem cells

Teeth comprise various mineralized components and pulp tissue that form during development via interactions between dental epithelial and neural crest cells. Combined, the tooth and the tooth-supporting structure called the periodontium form a functional unit that is planted in the alveolar bone of the maxilla or mandible [95]. Five different populations of human dental stem cells have been isolated and characterized: dental pulp stem cells (DPSCs), stem cells from exfoliated deciduous teeth (SHEDs), periodontal ligament stem cells (PDLSCs), stem cells from apical papilla (SCAPs), and dental follicle progenitor cells (DFPCs) [96].

Dental pulp stem cells can be isolated from permanent teeth and can differentiate into odontoblasts, adipocytes, neural-like cells, osteoblasts and myocytes [97] [95, 98]. Dental pulp stem cells were isolated from pulp tissues using an enzyme treatment and produced several colonies with different characteristics. The multipotential characteristics of dental pulp stem cells have made them an interesting source for regenerative medicine. Dental pulp stem cells were found to express mesenchymal stem cell markers such as CD73, CD90 and CD105. In addition, they were found to express CD13, CD29, CD44, and CD59.

There have been several reports that highlighted the ability of dental pulp stem cells to form dentin-like structures or to induce dentin thickening when implanted onto dental defects[99, 100]. The ability of dental pulp stem cells to promote bone regeneration has been tested in a clinical study. Human dental pulp stem cell-collagen sponge biocomplexes have been found to regenerate bone formation after injury caused by the extraction of the third molar [101]. DPSC implantation regenerated the impaired bone, along with the formation of new blood vessels[102, 103].

Stem cells from human exfoliated deciduous teeth are more readily available because they can be harvested from exfoliated teeth. These cells differ from DPSCs regarding their proliferation rate and cellular morphology. Unlike DPSCs, these cells are unable to form dentin pulp-like complexes. However, SHEDs have a high proliferative rate and an increased doubling population time compared with other dental stem cell types [104]. SHEDs can be obtained from the coronal pulp of exfoliated deciduous teeth. *In vitro*, they have been differentiated into several cell types, including neural cells, adipocytes, chondrocytes and odontoblasts [104-108]. *In vivo* analysis has shown that SHEDs can form dentin pulp-like tissue, odontoblast-like cells and bone [96].

Conclusions

Adult stem cells have many clinical and therapeutic applications that are addressing various unmet clinical needs for treating patients with various diseases related to heart, brain, bone, and skin, among other diseases, worldwide. Certain therapeutic approaches carried out using adult stem cells are not conventional because of their limited availability and differential proliferation potential. As there are many different types of adult stem cells, there is always the question of which stem cell type is more appropriate to use. The molecular and cellular mechanisms involving the pathways of these adult stem cells should be clearly studied and need to be revealed. Additionally, various safety issues should be clearly addressed before converting these therapies into clinical application. Continuous monitoring to see the improvement of patients injected with adult stem cells is necessary and can be performed by tracking these stem cells. Studies that improve the harvesting and delivering methods of adult stem cells to give cost-efficient outcomes are also of high demand.

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Conflict of Interest

The authors indicate no potential conflicts of interest.

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