MINI REVIEW

Stem-cell Transplantation: Potential Role in Therapeutic Modalities in Debilitating Diseases

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ABSTRACT

Stem-cell transplantation (SCT) is remaining as a major challenge for clinical applications in the effective treatment of many debilitating diseases. Enthusiastically, SCT inherits regenerative properties, hence offering unprecedented opportunities for the development of a lot of medical therapies of regenerative medicine. Newer approaches are under investigation to reprogram stem cells (SCs) that could be implemented as a therapy for a wide range of life-threatening diseases, namely, cardiomyopathy, diabetes, and cancer. Besides, a variety of SC-based treatment strategies is currently being explored for cell replacement therapies. Furthermore, Stem-cell therapy is being supported by several cutting-edge technologies and stringent standards of clinical research which immensely facilitated their implementation from bench to the clinic.

Key words: Debilitating diseases, stem- cells transplantation, therapeutic modalities

INTRODUCTION

SCT is still enduring a foremost challenge for their clinical applications in the management of many severely debilitating diseases, namely, autoimmunity, and brain injuries, genetic disorders, namely, thalassemia, immunodeficiencies, and cancer. Numerous scintillating pre-clinical and clinical discoveries on the identification of novel stem-cell populations, their usage, and supply of life-saving SCs have given excitement to articulate their regenerative capabilities for treatments of various diseases such as cardiomyopathy, Parkinson's, Alzheimer's, diabetes, cancer, including damaged organ site of the body.[1,2]

The sources of SCs could be classified into bone marrow cells, peripheral blood SCs, cord blood cells derived from related, or unrelated donors. SCs are totipotent, multipotent, and pluripotent. Totipotent SCs are capable to develop into any cell type found in the human body. Multi-potent SCs are essentially committed to producing specific cell types as well as a specific function.

Pluripotent embryonic SCs (ESCs) represent a potential unlimited *in vitro* source for all types of specialized cells and responsible to make up the human body. These cells are also ideally suited for studies of differentiation and early embryonic development. The ESCs are considered pluripotent cells which play a major role in the development of the embryo and are characterized by their differentiation to all cell types during embryogenesis. However, there may be a problem with genomic instability. Human pluripotent SCs, in particular, are immensely potential to generate pancreatic β-cells thus can be used in cell replacement therapy for diabetes.[3]

Adult SCs (ASCs) are also known as somatic SCs which are a rare population found in adult tissues and cannot multiply similarly ESCs. ASCs in specific niches can undergo multipotent differentiation. However, the use of these ASCs possesses considerable therapeutic potential for the regeneration of damaged tissues.

Mesenchymal SCs (MSCs) are present in the bone marrow and can differentiate into cell types such as osteoblasts, chondrocytes, endothelial cells, and probably also neuron-like cells.

Current revelations on the effectiveness of SCs unfolded a better understanding of regenerative medicine. Latest

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regulatory compliances are being enforced for the safest and most operative stem-cell transplants which can accurately benefit from debility to significant improvement in one's quality of life.

THERE ARE DIFFERENT TYPES OF STEM-CELL TRANSPLANTS

A mini-transplant is to prepare the patient for lower, less toxic doses of chemotherapy and/or radiation. The patient receives bone marrow and peripheral blood SCs which support a fewer toxic dose of chemotherapy and radiation. Similarly, a tandem transplant involves two sequential courses of chemotherapy. This comprises two sequential courses of high-dose chemotherapy and stem-cell transplant.

Allogeneic transplantation of hematopoietic SCs (HSCs) is commonly used in the treatment of various genetic disorders such as thalassemia and immunodeficiencies. In such type of SC transplants, the patient's bone marrow is subjected to the replacement with new, healthy bone marrow, or peripheral blood SCs from another person. Conventionally, most allogeneic stem-cell transplants are achieved using SCs from the bone marrow, but the use of peripheral blood SCs is also now commonly utilized. In this type of transplant, the SCs may also be utilized collected from another person with a matched immune system (human leukocyte associated antigens [HLA]-type). A donor could be related to the patient or an unrelated donor to the patient may also be used. New conditioning regimens such as reduced intensity SCT (RIST) have been evolved due to a low therapeutic toxicity.

HLA-mismatched transplantation is now successfully transplanted in haploidentical donors. It is, therefore, necessary to select the most compatible stem-cell source matched with the recipient condition as well as disease status. Allogeneic donor leukocytes can be used after non-myeloablative conditioning to exploit their graft-versus-tumor (GVT) as stem-cell therapy for cancer patients who are prone to relapse after autologous SCT.[4] In the past several decades, hematology has revolutionized the concept of bone marrow transplant into HSC transplantation, from allograft to autograft, from non-manipulated graft to hyper-selection, from hematopoietic cell therapy to immunotherapy.[4]

Hematopoietic stem-cell transplantation (HSCT) was first used as a treatment for some types of cancers, but now, it is widely used by many specialized clinics around the world to treat autoimmune diseases. Different cancers such as sclerosis, multiple myeloma, leukemia, and some lymphomas.[5] An extremely high success rate has been achieved for these treatment modalities. However, it is known as experimental. HSCT but not considered to be an oncological procedure. It is now known as a hematological process that involves the blood's role in health and disease. Recently, some outstanding changes have taken place in the current clinical practice of hemopoietic SCT for hematological diseases, solid tumors, immune disorders, and immune reconstitution after allogeneic stem transplants.[6]

Autologous transplantation of MSCs in the musculoskeletal system has been successfully explored in the regeneration of periodontal tissue defects, diabetes, critical limb ischemia, bone damage caused by osteonecrosis, burn-induced skin defects, and myocardial infarction 2, including the treatment of urinary incontinence and Duchenne muscular dystrophy.[7]

Autologous transplantation of peripheral blood progenitor mononuclear cells is also an ideal source of SCs for autologous transplantation because of technical advantages and more favorable engraftment kinetics in immunological reconstitution in cancer patients. In such transplants, the patient's bone marrow or peripheral blood SCs are collected, harvested, stored frozen until needed, and then transplanted back to the same patient after the completion of high doses of chemotherapy, radiation, or both to destroy your cancer cells. An identical twin could also be a donor for an autologous transplant.

Most of the stem-cell treatment modalities are being explored utilizing intravenous or direct injections. Furthermost, potential stem-cell treatment is achieved through a customized treatment plan. Since the disease status of the patient differs from each other, the treatment strategy must be personalized around their specific disease-related complications and symptoms of each patient.

In a syngeneic stem-cell transplants

SCs are transplanted to a patient from identical twins. Identical twins have the same genes, they also have the same set of HLA. As a result, there are less chances of the transplant being rejected.

RISK FACTORS ASSOCIATED WITH SCT

Allogeneic SCT may influence the patient's sexuality. It can also affect psychological factors such as staff-dependency, emotional, and distress, including physical factors, namely, hypoestrogenism, genital mucosae dryness, and occasionally vulval or vaginal chronic graft-versus-host disease (GVHD). Further, high doses of stem-cell therapy may promote neurogenesis. Hematopoietic stem-cell allogeneic transplantation can induce thrombocytopenia and hemorrhagic cystitis. New indicators are now emerging on the inheritance of disease-prone familial or mutational genes,

autoimmune disorders and amyloidosis for autologous, and solid tumors for allogeneic transplants.

CURRENT LIMITATIONS/ OBSTACLES IN SCT

Despite numerous innovative advancements in stem-cell transplant technologies, there are still many hurdles in stem-cell biology for their utilization in clinical applications, namely, inefficient differentiation, rejection of allogeneic cells, lack of specific methods of isolation, and enrichment of SCs.[8] It is assumed that the ability of de-differentiation or reverse lineage-committed cells to multipotent progenitor cells might overcome many of the impediments associated with using ESCs and ASCs in their clinical applications for robust strategies on SCT.

So far, it is still not clear whether SCs can proliferate extensively and generate adequate quantities of tissue? Does it remain to be determined whether umbilical cord blood HSCs are lived longer in transplanted recipients?

It is relevant to identify a silent, or mutational or inheritance of familial genes linked with diseases, intracellular signaling which induces SCs to become specialized and also to explicate exactly how SCs remain unspecialized and self-renewing for many years.

It is still not elucidated whether transplanted SCs would differentiate into the desired cell type (s) or not? Including their functions appropriately for the duration of the recipient's life or not?

It is also persisting a vital issue to understand whether the induced pluripotent SCs can help to circumvent issues of histocompatibility in transplants.

CONCLUDING REMARKS

Enthusiastically, numerous cutting-edge technologies have established that SCT possesses a unique regenerative property, thus offering extraordinary openings for expansion of a lot of medical therapies for debilitating diseases and also advancement in the innovative therapeutic of regenerative medicine.

The development of a new generation of regenerative medicine would rely on the widespread availability of reliable human cell populations to replace suboptimal diseases and to determine therapeutic potential.

Exploration of induced pluripotent SCs will immensely help reprogram diseased or damaged tissues and would resolve the issues of histocompatibility with donor/recipient transplants.

Engraftment kinetics are known to be linked with GVHD. Therefore, prophylactic regimens that control GVHD while maintaining GVT is needed to improve outcomes in heavily pretreated patients. We are optimistic to overcome these technical impediments? The possibility to overcome these impediments lies in patient-derived xenografts, which will evolve the new gold standard models for oncological drug development.

Novel technology that allows MSCs to maintain their SC function *in vivo* is critical for distinguishing the elusive SC from its progenitor cell populations. It is now envisioned that mesenchymal SCs can be used in systemic transplantation for generalized diseases, local implantation for local tissue defects, and also as a vehicle for genes in gene therapy protocols or to generate transplantable tissues and organs in tissue engineering protocols.

Transfer of drug resistance genes into HSCs would be a great potential for the treatment of a variety of inherited genes such as X-linked severe combined immune deficiency, adenosine deaminase deficiency, thalassemia, acquired disorders among breast cancer, lymphomas, brain tumors, and testicular cancer.

Some medical experts have opined that the advent of SCs research could be the greatest development when it comes to eradicating the sufferings of human health.

The development of nanomedicine in delivering cancer stem-cell therapies based on macromolecules or supramolecular aggregates will open up a new horizon of safer and more specific cancer therapies.

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