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Review Article

An Overview on the Biology of Stem Cells and Their Therapeutic Potential

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Abstract

Hematopoietic stem cell therapy (HSCT) has been around for many decades now and has become a household entity in the field of medicine. It has certainly enjoyed some success in improving clinical outcomes for various blood-borne malignancies and disorders. The discovery of HSCT was subsequently followed by the realization of the fact that vast reserves of stem cell therapy are still untapped. Much of the research work being conducted during recent times has shifted the focus of stem cells towards their use in providing therapeutic benefits in other areas as well. This includes using stem cell technology in diseases involving cells which are unable to undergo regeneration and repair (e.g. cardiac, nervous system and skeletal muscle disorders), the advantages of induced pluripotent stem cells (iPSCs) in alleviating the need for immunosuppression, the field of regenerative medicine which reprograms cells for effective tissue repair, utilizing adult stem cells and molecules released by them, treatment of serious and sometimes fatal autoimmune diseases and understanding the role of cancer stem cells (CSCs) in pathogenesis of malignancies. This article focuses on these multiple aspects of stem cell technology which have great therapeutic potential and might as well be the next major breakthrough to completely revolutionize the future of medicine.

INTRODUCTION

Stemcells area population of undifferentiated cells which possess the capacity of self-renewal, are able to differentiate into other cell types and can indefinitely divide themselves to produce more of the same type of stem cells. Human pluripotent stem cells are self-replicating cells derived from human embryonic or fetal tissue that can develop into cells of the three primary germ cell layers. The identification of adult stem cells for various types of tissues, their harvestation from bone marrow, peripheral or cord blood coupled with the ability to purify and maintain such cells in vitro, offers great therapeutic potential for many diseases for which conventional therapies haven't been quite successful. In addition, induced Pluripotent Stem Cells (iPSCs), a type of pluripotent stem cells can now be produced directly from mature adult cells and this has opened up a new window of opportunity for the future of medicine. By proving the presence of colony-forming cells (hematopoietic stem cells) in the mouse bone marrow, the Canadian scientists laid down the first bricks of the stem cell research foundation [1,2]. Stem cells are grouped in four broad categories: embryonic stem cells, fetal stem cells, adult stem cells, and induced pluripotent stem cells [3-5].

REVIEW

Clinical applications of stem cells

Hematopoietic stem cell transplantation is a widely practiced entity all around the world and has been in clinical use since some time now. It has shown a greater therapeutic success compared to other stem cell therapies such as those involving muscle or neuronal stem cells. Hematopoietic stem cell transplantation is being used to treat many blood-borne diseases such as leukemia, polycythemia vera, aplastic anemia, myelofibrosis, paroxysmal nocturnal haemoglobinuria etc. It commonly involves three types of grafts i.e. autologous, syngenic and allogenic grafts. The procedure involves bone marrow remission, harvest cell collection either from bone marrow or peripheral blood stem cells (mobilized with Colony Stimulating Factor), conditioning, stem cell rescue and regeneration. Still, nowadays, big hopes are laid in the direct differentiation of stem cells towards specialized

cell types such as pancreatic islets cells, neurons and cardiac myocytes [6-8].

While we've certainly come a long way in treating blood-related disorders using hematopoietic stem cell therapy, the focus of much of stem cell research today is in utilizing the amazing capacity of stem cells in treating certain resilient diseases which are proving difficult to control. These include a variety of malignant neoplasms, non-neoplastic but sometimes life-threatening autoimmune diseases and disorders associated with damage to cells with low or no regenerative capacity such as permanent cells like cardiac, nervous system and skeletal muscle cells.

Other than hematological stem cell transplants, there are several novel instances which use this advanced procedure. Hard tissue repair e.g. bone regeneration is a highly researched area where bone fractures are treated using stem cell-based therapies. Also ligament and tendon repairs in osteoarthritis and accidental injuries, joint repairs in osteoarthritis, muscle repairs in myocardial infarctions, nervous system repairs in spinal cord injury and peripheral nerve injuries and ophthalmological diseases such as corneal ulcers are newly rising areas with a potential for successful outcomes compared to the traditional methods currently in clinical practice.

Embryonic stem cells (hESCs)

Researchers have been successful in inducing human Embryonic Stem Cells (hESCs) to differentiate into cardiomyocytes in vitro, generating a possibility for effective cardiac repair. The US Food and Drug Administration (FDA) approved the first clinical trial involving human ESCs in 2009. The trial is being conducted by a company, 'Geron' and will evaluate the safety of embryonic stem cell-derived oligodendrocytes in spinal cord injury repair. GRNOPC1, Geron's lead hESC-based therapeutic candidate, contains hESC-derived oligodendrocyte progenitor cells that have demonstrated remyelinating and nerve growth stimulating properties leading to restoration of function in animal models of acute spinal cord injury. Their goal is for the application of GRNOPC1 in subacute spinal cord injury to achieve restoration of spinal cord function by the injection of hESC-derived oligodendrocyte progenitor cells directly into the lesion site of the patient's injured spinal cord. Additionally, the company is now also formally exploring the utility of GRNOPC1 in other degenerative CNS disorders including Alzheimer's, multiple sclerosis and Canavan disease. Hence, this technology, if successful in clinical trials has a huge potential to improve therapeutic outcomes associated with diseases involving cells, which under normal circumstances cannot undergo regeneration and repair. Transcription factors that play a key role in the molecular mechanisms of this process are: SOX2, NOTCH, WNT, PTEN, p53, Myc, as well as the ones from the HOX group [4,7,9,10], and Musashi-1 [9,10]. Multiple human Embryonic Stem Cell (hESC) lines have now been discovered and banking of clinical grade cells is underway. It would potentially lead to an optimum immunological matching of recipients and donors resulting in more successful treatment outcomes. Human embryonic stem (ES) cells are known to be derived from the inner cell mass of blastocyst., morulae and single blastomeres [11,12].

Fetal stem cells

The source of fetal stem cells is the fetal blood from umbilical cord and amniotic fluid, fetal tissues samples and the fetal adnexa such as fetal membranes and placenta.Fetal bone marrow, liver, kidney, lungs and also umbilical cord constitute other sources of fMSCs [13-15]. Fetal hematopoietic stem cells (fHSCs) and fetal mesenchymal stem cells (fMSCs) can thus be isolated. From the placenta, four distinct types of cells can be obtained: human amniotic epithelial cells (hAECs), human amniotic mesenchymal stromal cells (hAMSCs), human chorionic mesenchymal stromal cells (hCMSCs), and human chorionic trophoblastic cells (hCTCs). Studies show that human amniotic epithelial cells (hAECs) can differentiate towards all three germ layers, thus they are pluripotent [16].

fHSC transplantis used in patients who suffer from malignant hemopathies or metabolic storage disease as well as in the field of neuropathology (amyotrophic lateral sclerosis, cerebral palsy, cerebral atrophy, Huntington's disease and Parkinson's disease).

Induced pluripotent stem cells (iPSCs)

HiPSCs are pluripotent stem cells retaining the capacity to differentiate into cells that originate from all three germ layers. Induced pluripotent stem cells are a type of pluripotent stem cell that can be generated directly from adult cells by reprogramming them. Research related to induced Pluripotent Stem Cells (iPSCs) is increasing day by day as one of the advantages of transplanting iPSCs is that the patient's own cells can be used, thereby decreasing the need for immunosuppression. Patient-specific iPSCs also provide a new tool in discovering underlying mechanisms of disease which are presently unknown. These cells could be used in the future to cure diseases like neurodegenerative diseases, cardiac and metabolic conditions.

Tissue repair through cellular reprogramming in situ using stem cell-based therapy

Stem Cell-based therapy may play a significant role in regenerative medicine in future as well. It uses the principle of converting adult cells into other cell types for tissue repair and regeneration. Although isolated examples of adult cell reprogramming exist, there is a lack of general understanding about using this technology in a controlled and organized manner. This alternative strategy is used to direct cellular reprogramming without reverting to a pluripotent stem cell state. The basic principle is to stimulate a patient's endogenous stem cells in order to divide or differentiate, as would naturally occur during healing of a skin wound. A study has recently shown that exocrine cells of the pancreas in adult mice can be reprogrammed to become functional, insulin-producing cells which closely resemble endocrine beta cells using expression of transcription factors that regulate pancreatic development. The induced beta-cells cannot be differentiated from endogenous islet beta-cells based on their size, shape and histological features. The reprogrammed cells express genes essential for normal beta-cell function and can be used to treat hyperglycaemia as they secrete insulin and cause local vasculature remodeling. The concept of repairing tissue through a process of cellular reprogramming in situ using stem cell-based therapy is an area worth further exploration.

Adult stem cells

The main types of adult stem cells include hematopoietic stem cell (HSC) and mesenchymal stem cells (MSCs).More recently, Hematopoietic Stem Cell Therapy (HSCT) has been used as a form of high dose immunosuppressant in a select number of patients with autoimmune diseases that are resistant to standard therapies. Studies conducted previously on animal models have validated the use of HSCT in patients with this spectrum of disorders. Two randomised control trials have confirmed that HSCT is superior to monthly cyclophosphamide in treating systemic sclerosis with a highly significant disease-free and overall survival benefit shown in the Autologous Stem cell Transplantation International Scleroderma trial. Over 2000 patients worldwide with autoimmune conditions have been treated with HSCT with the two most common indications being systemic sclerosis and multiple sclerosis. This kind of treatment is used in patients who suffer from malignant hemopathies or metabolic storage disease that can benefit of allogenic transplant of hematopoietic stem cells [17,18].

MSCs are adult multipotent SCs that can be isolated not only from bone marrow stroma [19], but also from other tissues such as adipose tissue [20], neural tissue [21], olfactory mucosa [22], heart tissue [23], skin [24], gingiva [25], and many others. Classically, MSCs exhibit CD105, CD73 and CD90 as specific cell surface markers and lack expression of CD45, CD34, CD14 or CD11b, CD79 alpha or CD19 and HLA-DR surface molecules.

The possibility of using adult stem cells of various types and molecules they release e.g. microRNA in treating certain diseases is being highly researched as well. The advantage being that it avoids the issues associated with ESCs and iPSCs and is easier, more efficacious and less costly to develop and deliver to the patient. These molecules fit better into the current drug development model compared to the cell-based therapies leading to better therapeutic outcomes. Currently, there are two trials approved by Food and Drugs Administration (FDA) regarding the use of neural stem cells in patients that suffer from Parkinson's disease and spinal cord injury [27,28].

Cancer stem cells (CSCs)

Cancer stem cells (CSCs) are defined as cancer cells (found within tumors) that possess characteristics associated with normal stem cells such as self-renewal and can give rise to various cell types that comprise the tumor. They are tumorigenic (tumor-forming) and have been identified in multiple cancers e.g. blood, breast, lung, colon, pancreatic, CNS, skin, prostate and ovarian cancers. CSCs are often linked with tumor resistance to chemotherapy and radiotherapy which lead to the failure of standard therapies. Currently, most available therapies target the fast-growing tumor mass but not the slow-dividing cancer stem cells. Theoretically speaking if we are able to eradicate the origin of tumors i.e. CSCs we can quite possibly improve cancer survival, decrease recurrence rates and may even completely cure cancer patients. One possible method to achieve this is by producing drugs that selectively target cancer stem cells only, thereby removing the root of the tumor and causing less collateral damage to the patient's normal tissues as well. The development of specific therapies targeting CSCs provides a new hope for cancer treatment and cure especially in patients with metastatic diseases which, generally speaking have poor outcomes.

CHALLENGES IN STEM CELL RESEARCH

A brief summary of some of the challenges faced by researchers include stringent regulations, high expense, limited funding, mismatch in cost vs benefit compared to conventional therapies, safety improvements in the treatments, high failure rate of clinical trials, recruiting patients, need for new, high level clinical infrastructures and research centers and regulatory diversity across countries. Creation of unrealistic expectations and public controversies have played a part as well as denoted by the fact that stem cell based therapy has become questionable in relation to using this technology for human cloning.

CONCLUSION

Stem cell technology is a vast field of medicine, much of which is still in need of being discovered. Based on our current understanding and progression in this area, stem cells have abundant potential to provide medical advancements in future. A lot of research and clinical work is already underway to discover new ways of fully exploiting multiple aspects of stem cells in order to provide optimal therapeutic potential for humans. It is a ray of light for currently incurable diseases such as cancers, autoimmune diseases and cardiac, nervous system and muscular disorders. The goal of providing cure for these diseases is only possible if the medical community remains headstrong in facing and overcoming challenges which hinder progress. It is extremely important to continue the work being conducted on this budding technology which certainly promises to grow into a giant trunk with branches extending into multiple fields of medicine in future.

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