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Review Article

FUTURISTIC SCOPE OF STEM CELLS IN MEDICINE

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ABSTRACT

The most potential application of the stem cells (SCs) in human beings lies in their ability to regenerate cells and tissues. They differentiate themselves into specific cell type, thereby availing remarkable source of replacement cells and tissues. They differentiate themselves into specific cell types, thereby availing renewable source of replacement cells and tissues. Their potential of regeneration has now opened many avenues in the field of medical science and research. As a therapeutic adjuvant in near future, the SCs will emerge as an efficient technique to completely heal a number of diseases including diabetes, heart diseases and strokes, osteoarthritis, rheumatoid arthritis, and macular degeneration. The researches, which are underway, some of them will surely be proved as safe and effective SC treatment in the market in due course of time.

Keywords: Stem cells, Medicine, Embryonic cells, Heart disease.

INTRODUCTION

Advancing at an incredible pace with new discoveries in the field of stem cells (SCs) is flourishing each new day. In fact, in the current few years, the area of SCs research though has undergone rapid developments, throughout the time has been surrounded with controversies and debates. Currently, the field is promising new leads in the treatment of several incurable diseases. The capacities to regenerate and differentiate themselves, SCs give birth to a variety of specialized cells, i.e., totipotent cells, pluripotent cells, multipotent cells, and progenitor cells [1,2]. The characteristic, known as plasticity, varies depends on whether SCs originate from embryos or adult organism or any other sources. Having the enormous capacity to differentiate into other types of tissues, these specialized cells reflect the promising potential to usher in the area of regenerative medicines [3-5]. The field of SC research is still in its nascent stage. Though some advances have been made into understanding the underpinnings of basic biology and their differentiation into different cell lineages but still a long way to go. The SCs are characterized by their ability to differentiate into a different range of specialized cells for indefinite time. The presence of active telomerase in SCs provides them enormous potential to undergo cell division indefinitely while maintaining their undifferentiated state, the phenomenon called as self-renewal. Besides, they are able to differentiate into specialized cell types [6]. Depending on the signal and induced by a variety of growth factors, the skin, heart cells or neurons, or different types of other cells can be generated due to well-regulated different RNA/protein combinations and consequent differentiation [7].

HISTORICAL PERSPECTIVE

After so many failures, scientifically it demonstrated a successful culture and characterization of human embryonic SCs (ESCs) just over a decade ago. Since then, several new developments in the field of SC research occurred that has definitely changed the scenario. Development of induced pluripotent SCs (IPSCs) by introduction of a limited number of genes into the adult somatic cells has been a remarkable achievement and has paved the way for generation of patient-specific pluripotent SCs [8,9]. Though SC research began in mid-1800 in an unintentional way, with the discovery of some peculiar cells having self-renewal capability [10]. In 1900, again the field had gotten a breakthrough with the discovery of potent cells capable of generating blood cells. Bone marrow transplant using adult SC has been a great development in the SC research. In early 1900, a few unsuccessful attempts were made by administering the bone marrow by mouth. Further experiments on mice model clearly showed that bone marrow can be transplanted from one human being to another [11]. However, attempts on bone marrow transplant were failed among human beings. With the discovery done by Jean Dausset in 1958, by identifying the first human histocompatibility antigen (human leukocyte antigen [HLA]) opened a new era in the technique of marrow transplantation and engraftment [10,11]. The HLA proteins, normally present on the surface of mast cells of the body, provide the ability to discriminate between self- and non-self-proteins or cells. HLA can also be called as an integral component of the immune system, are proteins encoded by certain genes are also known as antigens. HLA genes are the human versions of the major histocompatibility complex genes, found in most vertebrates [12]. In 1960's, physicians transplanted successfully bone marrow between identical twins. In the same year, another success was achieved when researchers in the early to mid-1960s revealed that sexual organs of mice possess some unique cells that could give rise to various other kinds of cells. 1990's onward, many transplants were conducted with significant success rate to treat immunodeficiency and leukemia. In the year 1998, a historic discovery was accomplished by J. Thompson by introducing the first embryonic cell lines isolated from inner cell mass of early embryos. In the same year also, pluripotent germ cells were isolated by J. Thompson from the fetal gonadal tissues (primordial germ cells) [10,11,13].

Since 2007, several new remarkable achievements have been gained including the development of IPSCs. These cells are patient-specific, in growing cells without xenogenic feeder cell in a well-defined media free from fetal calf serum. However, still challenges are there in the characterization of cell product for therapy purposes.

VARIOUS TYPES AND SOURCES OF SCS

SCs are a type of cells that can regenerate themself to give birth to totipotent, pluripotent, multipotent, and progenitor cells. Totipotency of the cell is defined as a cells ability to transform into all types of the cells of an organism. To be totipotent is the most precious trait possessed by these SCs. Fertilized egg becomes totipotent blastomeres from its specialized cell types. Each cell is enough efficient to generate a complete organism (i.e., identical twins). While pluripotent cells

have the potential to develop into more than one type of mature cells depending on the signal. These cells are present in the undifferentiated inner mass of the blastocysts that can form nearly 200 different cell types. Multipotent cells are derived from fetal tissues, cord blood, and adult SCs, etc. Their ability to discriminate is more limited than pluripotent cells [14-16].

Based on the cell types or tissues of origin, SCs can be somatic SCs (SSCs) or ESCs. SSCs can be multipotent or unipotent having limited capability to differentiate [15,16]. ESCs are on the other hand pluripotent cells having an enormous capacity to differentiate into a variety of cells. IPSCs can be generated by reprograming of somatic cells [17].

Based on the cell type or tissue of origin, SCs can be somatic or ESC. With limited capacity, the SSCs are either multipotent or unipotent, whereas with multiple spectrum ESCs are pluripotent. Reprograming of somatic cells can lead to IPSCs.

SSCs

SSCs are a resident self-renewable population of cells present in all the creatures. Having limited plasticity, these cells are essentially undifferentiated residing in undifferentiated tissues. The cells are committed to the lineage of that organ. SSCs can be derived from various sources such as fetus, umbilical cord, placenta, infant, child or adult, and from different organs or tissues. Though their proliferation and differentiation capacities vary [18]. Umbilical blood initially discarded as medical waste is known to be a rich source of SCs. Banking of these SSCs, from this source, is getting more popular for its potential future use [19]. Bone marrow, being extremely rich source of SSCs, is drawn from spongy tissues, in the central core of bone. Bone marrow SCs are rapidly dividing cells; synthesize cells present in the circulation concerned with the fight against infection. This is being the most appropriate source of SCs, having very rich blood supply [18,20]. In the peripheral blood, the number of SCs is very less. They can be easily be trapped from the blood. Besides, all these menstrual blood also contain self-renewing SCs. Shedding from the endometrial lining present in the menstrual blood is much enriched in SCs containing millions of rich and abundant SCs. This source having rapidly dividing SC like bone marrow and would possibly prove to be a potential pool of SCs for a vast range of regenerative therapies. Menstrual SCs can differentiate in multiple types of SCs such as neural, cardiac, bone, fat, and cartilage [21]. The SCs derived from dental sites also very vast number. These SCs can be used for regeneration of entire tooth [22], for cleft palate [23], regeneration of nerve cells in Parkinson's disease [24].

As the abundance of SSCs in most of the tissues is relatively low, the number can be increased by prolonged culture or expansion technique, but equally, there is a risk of contamination with microorganisms and potential genomic alterations. These contaminants especially xenogenic pathogens may induce immune reactivity [20]. In bone marrow, GIT, and skin, these SSCs are incessantly divided throughout the life. However, in other organs, their induction occurs as per tissue repair or replacement demand. For carrying out research on SSCs, prior approval of Institutional Committee for SC research (IC-SCR) is required.

ESCs

Having totipotency capable of giving rise to the whole organism, ESCs are derived from pre-implantation embryos before differentiation of trophectoderm and inner cell mass. ESCs derived from ICM are pluripotent which can differentiate into ectoderm, mesoderm, and endoderm [25].

IPSCs

The IPSCs are generated from SSCs by a variety of genetic or epigenetic methods. The cells are efficiently capable of discriminating into ectoderm, mesoderm, and endoderm. Stimulated by appropriate stimuli, they can differentiate into lineage-specific progenitor and differentiated cells, i.e., neurons, cardiomyocytes, and many other tissues, but their tumorigenic potential is a major safety concern for therapeutic application [17,25].

RESEARCH IN SCS; RESTRICTED AND ALLOWED ASPECTS

India has done great progress in the SC research as is evident from work done in understanding the basic science and in the field of regenerative medicine. Creation of human embryonic cell line is another example of the efforts done in this direction. A number of publications both in reputed national and international journal have been contributed by the stalwarts working in the area. The outcomes of their work are definitely moving toward translational research and thereby to clinical practice in our country. There are still certain aspects are there to look upon for successful implementation of uses of SCs. In terms of regulations, there are certain standards available currently in the country for conduction smooth and hassle-free clinical research.

In vitro studies on pluripotent SC lines, i.e. ESCs or IPSCs or SSCs from fetal or adult tissues, for understanding basic biology or *in vivo* studies using these cells lines may be carried out with prior approval of IC-SCR. *In vivo* experiments require a preclinical evaluation of efficacy and safety of human SCs or their derivatives. Ethical guidelines have to be followed or considered for research on ESCs with prior registration with National Apex Committee for SC Research and Therapy through IC-SCR. For SC line from source outside, the country should follow National Guidelines as per this document.

Creating human zygote by *in vitro* fertilization, somatic cell nuclear transfer, or any other method with the specific aim of deriving SE line for any purpose will require to have minimum number of embryonic blastocysts. The research team involved should have appropriate expertise and training in derivative characterization and culture of ESCs. A clinical trial using cells derived from differentiation of human ESCs or IPS cells or any SC after major manipulation shall require the approval of DGCI after obtaining approval from IC-SCR and IEC. Research related to human germline, gene therapy, and reproductive cloning are strictly prohibited. *In vitro* culture of intact human embryo, beyond 14 days of fertilization or formation of primitive streak is also not allowed. Clinical trials involving the transfer of xenogenic cells into human host, any clinical research on xenogenic human hybrid or research involving implantation of human embryos into the uterus after *in vitro* manipulation at any stage of development in human beings or primates is strictly not allowed [26].

Futuristic scope

The therapy holds great promise and potential in the field of regenerative medicine in near future. In coming years, this therapy is going to be the major medical treatment for a number of challenging diseases, in which cure is almost impossible presently. Field of SCs in regenerative medicine is rapidly expanding its wings toward translational research and eventually to clinical practice in India. However, still there are certain issues to be looked at for successfully implementing its applications in clinical practice. Our prime concern should be to determine the tissue source and type of SCs or differentiated cells that have got most appropriate traits to cure a specific disease. Strict preclinical models for determining efficacy, safety, toxicity, delivery routes, and techniques should be tested to ensure safe and efficacious to conduct the clinical trial. Moreover, for the sustenance of engraftment, allogeneic SC transplantation, immunological barrier must be overcome.

SCs are like body's own repair kit. They can metamorphose into various cell types of our body. Well, ESCs are much of fray because of their broader spectrum, but IPSCs, which can be created by reprograming somatic cells and also provide potent platform for allowing researchers to see course of disease development in human beings.

Though recent development of IPSC suggests some of the specific factors involved in transforming SSCs to IPSCs, the technique must be adopted to introduce these factors in a well-controlled manner into the cells.

SCs in future treatment of heart diseases

In current time, cardiovascular diseases are one of the leading causes of death in the United States and other countries. In an oxygen-deprived heart tissues, there occur injury and scaring. Cardiac cells become overloaded with blood flow and overstretching to sustain cardiac output, lead to heart failure. If quick measures are not being taken, may eventually lead to death. Restoration of heart tissues through regeneration using embryonic and adult-derived SCs is indeed an exciting area of research. Not only these, various other SCs derived from umbilical cord blood cells, endothelial progenitor cells, and SCs derived from other sources have been well experimented on various animal models [27]. In a study, SCs were drawn from patient's own bone marrow and then injected in the scar affected portion of the heart. And within 6 months patient had improved heart pumping function [28]. In another recent new clinical trial conducted in March 2014, 59 patients with severe heart failure were chosen for study. Out of them, 39 patients were given injections of SCs into heart muscles through a catheter inserted in the groin. The procedure required local anesthesia. While remaining control patients were on saline injection. Patients on SCs therapy experienced an 8.2 ml decrease in end-systolic volume. They also experienced a reduction in heart's scar tissues compared to control. Control group showed 6 ml increase in the systolic volume [29].

However, to assess the safety and efficacy issues in the clinical practice, there is essentially need of more and more refinement. The outcome of the studies done in the direction indicate, how 1 day SCs may be used to repair damaged heart tissues.

NEW HOPES FOR THE CURE OF DIABETES

Diabetes is another disease grasping a significant part of the population of the world. People, suffering from Type 1 diabetes, have their pancreas is though secreting appropriate amount of insulin, but due to autoimmune reasons the insulin is destroyed by its own immune system. Doug Melton, Xander University Professor at Harvard University, using human ESCs as a starting point, for the first time been able to create human insulin-producing beta cells equivalent in almost every way to normally functioning beta cells. The SC-derived beta cells are currently undergoing trials in animal models, including non-human primates. Experiments were reproduced in large quantities needed for cell transplantation and pharmaceutical purposes [30]. The SC-derived beta cells are currently running trials in animal models and non-human primates [31]. Newer studies done in the direction clearly show that in near future, it might be possible to exploit human ESCs via cell culture and various other techniques to form insulin-producing cells that can finally be used in transplantation therapy [32].

Hematopoietic SC (HSC) transplantation

Chemotherapeutic agent used in the treatment of leukemia and lymphoma would drastically impact healthy cells along with the leukemic or neoplastic cells. Over the years, bone marrow transplant has been used for such types of disease treatment [18-20]. The treatment also generates an immune response that helps to kill cancer cell as well. Graft versus host disease is the most serious side effect of this treatment. Prochymal therapy has been introduced for the management of graft versus host disease in children who are not responsive to steroids. Mesenchymal SCs (MSCs) derived from bone marrow of adult donor are purified from marrow, cultured, and packaged up with 10,000 doses. Doses are frozen until needed. Scientists are experimenting with different research strategies to generate tissues that will not be rejected. Fully matured human red blood cells (RBCs) can also be generated by *ex-vivo* HSCs (precursor of RBCs). In this methodology, HSCs are grown in an environment that mimics the conditions of bone marrow. Erythropoietin is added to induce facile transformation of HSCs to RBCs [33]. The technique would have future potential benefits in the field of gene therapy, blood transfusion, and topical medicine.

Neurodegeneration and SCs

Healthy adult brain is having a number of neural SCs. These cells divide and redivide to become progenitor cells. These progenitor cells roam around the brain to maintain the neural population. It has been well reported in the literature that pharmacological activation of these endogenous SCs may induce neuroprotection and behavioral recovery in the rat model. In another report also, the brain of a stroke patient was injected with SCs [34]. Research in the area is underway and in the near future, will pave the way to treat brain degeneration in Parkinson's, amyotrophic latent sclerosis, Alzheimer's diseases, and other complicated disorders [35].

SCs in wound healing

In case of wounded tissues, a possible way for tissue generation is in an adult is to place adult SC "seed" inside the tissue root and allows its differentiation in the tissue bed cells. The method seems to be similar to the regenerative response in fetal wound healing. SC research for wound healing is moving along a number of different ways. Some of the ways have been transformed into early Phase I and Phase II trials. One of the ongoing concerns is the treatment among the aged people. Collection of the SCs would not be the viable option in elderly people as SCs pool is decreased as age advances [36,37].

Orthopedics and SCs

The bone marrow stromal cells are a type of MSCs that in an appropriate environment are capable to differentiate into musculocutaneous cell types which can be the tool for synthesis of bone, tendon, articular cartilage, ligaments, and part of bone marrow [38]. A report has been published describing correction of nine defects in fine knees involving transplantation therapy with MSCs [39]. MSCs are currently under clinical trial as possible treatment of graft versus host diseases. Recently, US-based SC clinics have treated patients with their own bone marrow or adipose derived adult SCs as part of clinical trial [40]. With more advanced knowledge of tissue engineering, SCs procedure will become part of routine service to the society.

CONCLUSION

There are many challenges ahead, but in near future, definitely SCs therapy will be as common as any medicine to a patient. The researches, which are underway, some of them will surely be proved as safe and effective SC treatment in the market. ESCs undoubtedly are the key research tool to understand fundamental key events in embryonic development and various birth defects. The clinical scope of the SCs seems endless. The futuristic scope of these novel cell-based therapies for various pervasive and debilitating diseases is dependent on successful differentiation, transplantation, and engraftment. Through extensive researches in the fruitful direction, the SCs must be ideally made to proliferate extensively and generate sufficient quantities of cells making tissue, to differentiate into desired cell type, and to survive in the recipient after transplant. Only further research and its wider applications will solve many practical and theoretical queries concerned with SCs.

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