Stem cells: Frontier in disease research and development

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ABSTRACT

Understanding about the cellular therapeutic approaches has improved since last few years which has paved the way towards its therapeutic applications in the treatment of several incurable diseases. These approaches should be easily accessible to the patient’s as quickly as possible. Various landmark discoveries have done since last decades. However, suitable source, defined cell number and phenotype are still not clear that faint the strategy prior to application. Cellular reprogramming using somatic cell nuclear transfer (SCNT) provides a significant tool to overcome these hurdles by producing large number of functionally motivated cell phenotypes suitable for biopharmaceutical screening and creating stem cell lines as disease modules. Therefore, this review describes the current catalogue of human disease specific cells productions tools to overcome traditional sources and modules.

Keywords: Embryonic stem cells; adult stem cells; SCNT; induced pluripotent stem cells; therapeutic potential
1 INTRODUCTION

One of the most exciting frontiers in stem cell biology and medicine is the potential use of stem cells for the treatment of various developmental or degenerative diseases for which there are no cures. Nowadays it is well known that most tissues in the body continuously generate new cells either to replace the damaged/lost cells or to fulfill the increased demand [1]. The ability of a tissue to renew and repair itself depends on small group of cells called stem cells. These cells exist throughout life in close proximity with nurse cells which provide them required growth factors and signals that helps to maintain the unique property of the stem cells-the capacity of self-renewal, long-term viability and multilineage potential [2].

Therefore, stem cell applications in regenerative medicine are being developed to regenerate tissues and repair failing organs. Research developments towards stem cell biology and regenerative medicine have proved the potential use of different types of stem cells in the treatment of various degenerative diseases such as Alzheimer disease, Parkinson’s disease, muscular dystrophy, brain trauma, spinal cord injury, myocardial infarction, critical limb ischemia, diabetes, stroke and cancers [3]. In clinical practice choosing suitable stem cell sources, use of advanced cell culture techniques, characterization, in vitro and in vivo behavior raises several controversies for using these cells [4]. Therefore, before transferring the experimental therapy into human, beneficial experimental data in suitable animal models should be provided for the treatment of particular disease which should insure the proper cell integrity, viability and route of delivery.
Since the stem cells research started, many sources have been used to isolate these types of cells in stem cell research and development. In a broad way according to the developmental status of the individuals, stem cells are classified into two major categories; embryonic stem cells and adult stem cells [5].

1.1 Embryonic stem cells

The successful conception of human embryonic stem (ES) cells in 1998 opened the door to an important new area of biomedical research [6]. ES cells are unique biological entities that have the ability both to reproduce themselves endlessly and to give rise to all specialized cell types of the body. These cells are derived from the blastocyst-stage of early mammalian embryo and are characterized by their capacity for prolonged undifferentiated proliferation in culture while maintaining the potential to differentiate into derivatives of all three germ layers [6]. Several studies have been demonstrated in vitro spontaneous and directed differentiation systems for human ES cells into several lineages, including cardiac tissue [7], neuronal tissue [8], β islet pancreatic cells [9], hematopoietic progenitors [10], and endothelial cells [11]. Therefore, a key challenge for ES cell scientists is to control its differentiation into desired cell types. Guided by various researches in basic developmental and stem cell biology with post-genomic information and technologies, researchers are trying to get more knowledge to understand the mechanisms that maintain self-renewal of ES cells or direct their differentiation [12].

Concluding the whole ES cell research, it is still in its infancy and the scientific challenges in harnessing the potential use of these cells is not over yet and need to understand the uncertainty in genetic stability of these cells during long-term expansion. Therefore,
comprehensive monitoring is required prior to any clinical applications of ES cells either in animal models or in human. To overcome these difficulties sophisticated bioprocessing techniques and novel mechanisms such as Somatic cell nuclear transfer (SCNT) will be required to enable large scale production of functionally mature phenotypes suitable for biopharmaceutical screening and for funding multi-centre clinical trials in the absence of major industry partners [13, 14]. These hurdles should be overcome by a combination of individual scientific creativity and Europeanwide co-ordination and investment.

In brief, ES cells provide unmatched opportunities for applying post-genomic technologies to understand the exact mechanisms of cellular development, functional differentiation and disease treatment. Out of this should emerge complete medical benefits in the form of new biomarkers, improved drugs, and ultimately cell replacement therapies.

1.2 Adult stem cells

Adult stem cells are regenerative cells of the body that possess the characteristic of plasticity-the ability to specialize and develop into other tissues of the body. They are found in our own organs and tissues such as fat, bone marrow, umbilical cord blood, amniotic fluid, placenta, brain, and olfactory tissue [15, 16]. This simple fact has remarkable implications for medicine-diseased or damaged tissue can become healthy and robust through the infusion of such cells. This has consequently commanded the attention of many researchers as well as those suffering from disease.

With adult stem cells, physicians have successfully treated autoimmune diseases such as lupus, multiple sclerosis, Crohn's disease, and rheumatoid arthritis [17-19]. Furthermore, adult stem cells have helped to avert corneal degeneration and to restore vision in cases of
blindness [20]. They have also restored proper cardiac function to heart attack sufferers [21] and improved movement in spinal cord injury patients [22].

2 CREATING PLURIPOTENT STEM CELLS

In addition to stem cells that are isolated from the body, scientists have found a way to create stem cells by using various reprogramming techniques in the laboratory. Two such reprogramming techniques are the creation of induced pluripotent stem cells and the use of SCNT. In 2009, a Canadian-Scottish research team led by Andras Nagy was the first of several teams to develop a method to create induced pluripotent stem cells (iPSCs) without the use of retroviruses [23, 24]. This development could lead to greater application of iPS cells, which are a less controversial source of stem cells. Continuing research using iPS cells is needed in order to determine whether iPS cells are as malleable as human ES cells, but also because iPS cells may be an extremely powerful tool for creating stem cell lines as disease models.

2.1 Somatic cell nuclear transfer (SCNT)

SCNT involves removing the genetic information from an unfertilized egg and replacing it with the genetic information from a cell taken from the body of the person under investigation [25]. The potential of this approach is to provide opportunities to study inherited diseases in which the genetic cause has not been identified such as motor neuron disease (MND), amyotrophic lateral sclerosis (ALS) or Lou Gehrig’s disease [26].

The approach to studying such type of inherited human diseases using a clonally expanded and in vitro differentiated population of stem cells involves three major steps: 1. use of
somatic cell nuclear transfer (SCNT) to produce a single cell resembling a fertilized human egg. 2. derivation of ES cells from that cell; 3. culture from that cell line of the specific type of cell that is affected in the disease (Figure 1).

Figure 1 Schematic representation for the process of somatic cell nuclear transfer (SCNT)

Failure to derive stem cell lines from SCNT embryos may reflect the limitations of the present procedures for SCNT. SCNT is an example of noble methodology used in manipulating the ES cell research and treatment of serious degenerative inherited diseases, and further more applicable methodologies are need to be discovered for the pharmaceutical industry that could improve the lives of millions.

3 HISTORICAL PERSPECTIVES OF STEM CELL RESEARCH

In the mid 1800s when it was discovered that cells are the building blocks of the life and has potential to produce other body cell types, has emerged a new field of investigation to know the functional aspect of the cells. In order to this in 1900s, attempts were made to fertilize mammalian eggs outside of the human body and it was found that some cells have
the ability to regenerate blood cells. After identification of stem cells in human cord blood in 1978, various key investigations and developments have been included in the stem cell research (Table 1). Since then various national policies and debate amongst the public and religious groups, government officials and scientists have led to various laws and procedures regarding stem cells harvesting, development and treatment for research to disease purposes. Such policies have made the stem cell research to safeguard the public from unethical stem cell research and use while still supporting new advancements in the field.

Table 1 History and milestone discoveries in stem cell research

<table>
<thead>
<tr>
<th>Year</th>
<th>Major Discoveries</th>
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<tbody>
<tr>
<td>1878</td>
<td>The first attempts were made to fertilize mammalian eggs outside the body</td>
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<tr>
<td>1959</td>
<td>First animals made by in-vitro fertilization (IVF)</td>
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<tr>
<td>1960</td>
<td>Eratocarcinomas determined to originate from embryonic germ cells in mice. Embryonal carcinoma cells identified as a kind of stem cell</td>
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<tr>
<td>1968</td>
<td>The first human egg is fertilized in vitro</td>
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<tr>
<td>1970</td>
<td>Embryonic stem cells injected into mouse blastocysts make chimeric mice. Cultured SC cells are explored as models of embryonic development in mice</td>
</tr>
<tr>
<td>1978</td>
<td>Stem cells were discovered in human cord blood</td>
</tr>
<tr>
<td>1981</td>
<td>First in vitro stem cell line developed from mice</td>
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<tr>
<td>1988</td>
<td>Embryonic stem cell lines created from a hamster</td>
</tr>
<tr>
<td>1994</td>
<td>Human blastocysts are generated and the inner cell mass is maintained in culture. ES like cells form in the center and retain stem cell like morphology</td>
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<tr>
<td>1995</td>
<td>First embryonic stem cell line derived from a primate</td>
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<tr>
<td>1997</td>
<td>Cloned lamb from stem cells and Leukemia origin found as haematopoietic stem cell, indicating possible proof of cancer stem cells</td>
</tr>
<tr>
<td>2005</td>
<td>Embryonic-like stem cells found in umbilical cord blood</td>
</tr>
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2006  Mouse induced pluripotent stem cells

2007  Stem cells identified in amniotic fluid

2008  Successful cartilage regeneration in the human knee using autologous adult mesenchymal stem cells and Embryonic-like stem cells were identified from a single human hair

2009  Yong Zhao and colleagues confirmed the reversal of autoimmune-caused type 1 diabetes by Cord Blood-Derived Multipotent Stem Cells (CB-SCs) in an animal experiment

2010  Transplanted cells that contain their new host's nuclear DNA could still be rejected by the individual's immune system due to foreign mitochondrial DNA. Tissues made from a person's stem cells could therefore be rejected, because mitochondrial genomes tend to accumulate mutations

2012  Mouse skin cells were used to create stem cells and then used these stem cells to create mouse eggs. These eggs were then fertilized and produced healthy baby offspring. These latter mice were able to have their own babies

4 EVALUATION OF THE THERAPEUTIC POTENTIAL OF STEM CELLS

The field of stem cell research is needed to move forward towards the new therapies that can be easily available to patients as quickly as possible. There is much evidence from pre-clinical studies pointing to the effectiveness of stem cell delivery [27, 28]. A few small human studies have also been published, mainly on patients with heart failure, which suggest that stem cells offer new hope to patients [29]. There is an optimistic perspective about stem cell therapy that it will be effective in a broad spectrum of diseases as many advanced research projects are underway in different parts of the world and many governments have made a decision to invest very large proportions of Research and Development (R&D) budgets in stem cell research (Figure 2). Now is a good time to set stem cell therapy in a realistic perspective and examine current scientific and clinical approaches.
Schematic representation showing the potential sources and therapeutic applications of embryonic and adult stem cells. The pluripotent ESC types derived from blastocyst during embryonic development and multipotent tissue-resident adult stem cells arising from ectoderm, endoderm and mesodermal germ layers are shown. The pathological disorders and diseases that might benefit the embryonic and tissue-resident adult stem cell-based therapies are indicated.

Abbreviations: BASCs, bronchioalveolar stem cells; bESCs, bulge epithelial stem cells; CESC, corneal epithelial stem cells; CSCs, cardiac stem cells; eNCSCs, epidermal neural crest stem cells; ESCs, embryonic stem cells; EPCs, endothelial progenitor cell; HOCs, hepatic oval cells; HSCs, hematopoetic stem cells; KSCs, keratinocyte stem cells; MSCs, mesenchymal stem cells; NSCs, neuronal stem cells; PSCs, pancreatic stem cells; RSCs, retinal stem cells; SKPs, skin-derived precursors.

There are numerous reports in the scientific literature describing the successful results of experiments on stem cell delivery in animal models of disease [30-36]. In many cases the
studies are well conducted, carefully interpreted and subject to the sort of stringent review that we expect.

4.1 Nervous system diseases

Many nervous system diseases result from the loss of nerve cells. Mature nerve cells cannot divide and replace lost cells. Without regeneration of lost nerve tissue, no therapeutic possibility exists. In Parkinson's disease, nerve cells secreting dopamine die. In Alzheimer's disease cells that make other neurotransmitters die. In amyotrophic lateral sclerosis, motor nerve cells that activate muscles die. Many different types of cells are lost in other injuries such as spinal cord injury, brain trauma, and stroke. Furthermore, glia, the cells that protect nerve fibers are lost in multiple sclerosis. Creating new nerve tissues from pluripotent stem cells offers a potential therapy for these diseases.

4.2 Primary immunodeficiency diseases

Diseases such as severe combined immunodeficiency disease, Wiskott - Aldrich syndrome and the autoimmune disease lupus, as well as AIDS, all characterized by an unusual susceptibility to infection, have the potential to be treated by stem cell therapies. Pluripotent stem cells could be used to regenerate the missing immune cells of virtually all primary immunodeficiency diseases. The transplantation of stem cells reconstituted with the normal genes could restore immune function and a normal quality of life for these people.

4.3 Diseases of bone and cartilage
Stem cells could be used to differentiate and correct many degenerative conditions of bone and cartilage. This therapy also holds promise for genetic disorders such as osteogenesis imperfecta and chondrodysplasias, as well as for conditions resulting from physical damage such as osteoarthritis and bone fractures.

4.4 Tooth regeneration

After discovering the potential of stem cells to cultivate a complete tooth in mice in 2004, confidence was induced about the technology which can be used to grow live teeth in human patients. Since then various sources of stem cells have been tried to regenerate teeth by inducing various factors. In theory, stem cells taken from the patient could be coaxed in the lab into turning into a tooth bud which, when implanted in the gums, will give rise to a new tooth, and would be expected to grow within few months. Many challenges remain, however, before stem cells could be a choice for the replacement of missing teeth in the future.

4.5 Cancer

Various types of cancers have emerged as life threatening diseases which need to be treated as soon as possible. Identification of cancer stem cells concept has emerged an effort to provide better treatment strategies. Such as in leukemia, bone marrow stem cells are injected into a recipient following chemotherapy. This is an attempt to restore immune function after virtually destroying. Unfortunately, these recovered cells have a limited ability to differentiate and restore immune function completely in this setting.
Besides all these major diseases stem cell therapy is spreading its areas and advancements in several other diseases such as diabetes, deafness, blindness, muscles repair, tendon repair, infertility, birth defects, liver damage repair, cardiac failure, and birth defects etc. The growing researches and advancements in stem cell therapy will definitely provide a better solution for treating these diseases in human welfare.

5 MAJOR CHALLENGES

Stem cell research has undergone vast advances in the past few years. This does not mean, however, that researchers have not faced the apportion of problems. It has proved various types of challenges for scientists to ensure the long term proliferative ability and pluripotency of different types of stem cells. These are important characteristics to maintain, as accurate models required understand the unique genetic and molecular basis by which these cells are able to replicate indefinitely. In addition to providing accurate models, culturing stem cells in vitro is also crucial in order to ensure that sufficient quantities of stem cells are available to treat specific diseases.

Teratoma formation has also produced a hurdle that needs to be overcome. Formation of tumor like masses of cells at injection sites significantly limits the therapeutic potential applications of various types of stem cells.

Immune challenges also prove a significant barrier to the application of stem cell therapies. If the stem cells are recognized as non-self, they will be rejected and destroyed. Two potential solutions to this problem have been proposed. One solution is the creation of universal donor stem cells through genetic engineering techniques. Theoretically stem cells could be created that lack outer surface labels. The absence of these labels, which normally
identify cells as non-self, would eliminate the problem of immune rejection. Another solution to immune rejection would be to engineer stem cells identical to the recipient's cells, using the patient's own DNA. The former solution of universal donor stem cells, however, would prove less labor intensive and more cost effective, than the latter solution.

Adult stem cells have also presented unique problems of their own to researchers. In addition to proving challenging to maintain in culture, like embryonic stem cells; they have proven quite rare in adult tissues and need to isolate and identify for therapeutic applications.

6 CONCLUSIONS

All of this research contributes to a rapidly growing stem cell database, and is critical to support this type of work to be continued. However, there is a need of caution for the development of stem cell therapy with sensible awareness of the issues to treat various human degenerative diseases. As the tremendous promise of stem cell technologies research, with the possibility of products that could revolutionize the treatment of diseases and conditions, the potential for profit is staggering. Tempering this exuberance, however, are the ethical, legal, political, and financial challenges that face this field of research. The eventual resolution of these conflicts will determine the success of stem cell research and potentially the face of medicine in the future.

7 Acknowledgements

None
8 Conflict of interest

None

9 References


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