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A Review on Stem Cells: A New Toll in Diseases Therapy

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ABSTRACT

Stem cells are known as special somatic cell types that have the ability to self-renew and differentiate into various types of cells. They are categorized into two major groups such as embryonic stem cells and adult stem cells. Embryonic stem cells are pluripotent, which have the potency to differentiate into almost all cell types and grow up from the mesoderm, endoderm, and ectoderm germ layers at the beginning stages of embryo. While adult stem cells can be pluripotent or multipotent, which can differentiate into the family of a closely related cells. Over few decades, researchers have been studying and exploring new ways to treat different types of diseases like Parkinson's and Alzheimer's disease by using stem cells. Hence, embryonic and adult stem cells have been widely used in stem cell therapy. Here, we elaborate the problems of using embryonic stem cells and adult stem cells in stem cell therapy and its possible solutions, and discuss the applications of both stem cells types in biology-based field including disease modelling, regenerative medicine, drug discovery and cytotoxicity studies.

Keywords- Stem cells, Disease modelling, Regenerative medicine, Drug discovery, Cytotoxicity.

I. INTRODUCTION

In multicellular organisms, special somatic cell types are existed and called as stem cells [1]. Stem cells have the potency to switch or differentiate to various cell lineages and eventually to a tissue or a complete organ. They can be found in all living existence, from the time of embryo to the end of life. Stem cells have the ability to produce indefinitely copies of itself through mitotic cell division and can differentiate specialized cells for our body tissues. Stem cells are important for the development and repair of our brains, muscles, nerves, bones, blood, skin, and other organs. Stem cells can be classified into two main groups, embryonic and adult stem cells [2]. Embryonic stem cells (ESCs) grow up from inner cell mass of a blastocyst embryo, and it's called pluripotent stem cells too. These cells derived from human embryo after 4 or 5 days of egg fertilization [1]. Adult stem cells (ASCs) are called undifferentiated cells, and they have important role in human body to regenerate damaged tissues and repair those tissues in which they are found [2].

It has been clearly stated that all types of stem cells have important role in medical research [2]. However, the first productive contribution in stem cell research was made in early 19 century by Russian histologist Alexander Maksimov when he realized that some cells can generate other types of cells. And, since then stem cell held is under investigated particularly in medical science to utilize the stem cells as alternative tool to cure various disease with the term known as stem cell therapy [1]. Researchers have interest to study stem cell biology to find new ways of treating health problems, and it is one of significantly issue for them. Fortunately, the culture of stem cells is easy nowadays for scientific researchers, and can be transformed into various tissues like nerves and muscle tissues [2]. How a single cell changes to an organism and how a healthy cell replace damaged cell in adult organism are reasons that need to advance knowledge and continues research on stem cells [2]. In this review, we describe the

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challenges and solutions towards using ESCs and ASCs in stem cell therapy, and discuss the applications of ESCs and ASCs in biology-based fields including disease modelling, regenerative medicine, drug discovery and cytotoxicity studies.

II. CHALLENGES OF USING ESC IN STEM CELL THERAPY

Recently, ESC have been used in stem cell therapies including human umbilical cord mesenchymal stem cells and cardiomyocytes that derived from human embryonic stem cells due to its pluripotency and ability to self-renew [3,4]. Many stem cells therapies have been done using mice model and produced successful results. For an example, a study showed that the attempt of using ESC in stem cell replacement therapy was successful for Parkinson's disease by generating dopamine neurons of a mice [5].

However, one of the challenges of using ESC in stem cell therapies is ethical and legal issues constraints when using human embryos. Research using hESC might cause several ethical issues including destruction of embryos, medical risk for oocyte retrieval, payment to oocyte donors and protection of woman reproductive interest in infertility treatments to create embryos especially for research purposes. Medical risks that woman might suffer upon oocyte retrieval are ovarian hyperstimulation syndrome, bleeding and infection [6]. Besides, transplantation of ESC into mouse model can lead to malignant tumors and death. It has been stated that teratomas are formed by residual undifferentiated ESCs in the cell preparation of immunodeficient mice. Other challenges that can be encountered in stem cell therapy are on how to prevent cancer risk and minimize contamination during research [7]. Furthermore, ESC only allows allogeneic tissue transplantation techniques [8].

III. SOLUTIONS TOWARDS CHALLENGES OF ESC IN STEM CELL THERAPY

Several strategies can be taken to overcome the challenges towards using ESC in stem cell therapy including providing informed consent form in ESC clinical trials and oocyte donation, and protecting confidentiality of donor information. Medical risks for oocyte retrieval can be reduced by observing the number of developing follicles and optimising the dose of human chorionic gonadotropin specific for ovulation induction. Reimbursement to oocyte donor is a solution for payment, which can prevent the ethical problems of it. Infertility care must be provided for the IVF patients and the physicians should not know about the patient's agreement on oocyte donation for the embryonic stem cell research [6]. The recent embryonic stem cell research involved with formation of organoids such as intestines, stomach, retina, brain and liver for drug testing and transplantation purpose. Schematic representation of organoid generation by isolation of embryos or derived from pluripotent stem cells is shown in Figure 1. The advantages of using organoids are specific patient of 3D cell culture and they are in vivo-like complexity and in vivo-like architecture.

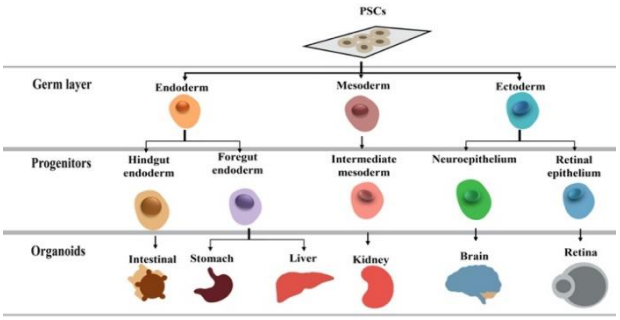

Figure 1: An overview representation of organoid generation from embryos or derived from pluripotent stem cells (PCS).

IV. CHALLENGES OF USING ASC IN STEM CELL THERAPY

Adult stem cells (ASCs), which mostly come from hematological, mesenchymal, epithelial, and neural cell lineages, are currently the main source of cells examined in tissue regeneration. Mesenchymal stem cells (MSCs), which have significant proliferative power, paracrine effects, multipotent differentiation potential, immunomodulatory capacity, and profiles of cell surface markers, are the most often used source in cell therapy.

However, maintaining stem cells' survival, characteristics, and functionality before and after implantation in vivo is the main challenge with stem cell treatment. Once isolated from the native tissue milieu, stem cells quickly lose their niche and function. Cells lifespan are shortened due to over-expansion in vitro and cellular DNA tends to be instable during long-term culture due to telomerase activity [9]. Using these cells to implant in the host will lead to low rates of cell survival, poor outcome in-growth, homing, differentiation and paracrine effects [10]. ASCs also have the potential to form teratoma or tumors and a relative degree of difficulty in extracting viable stem cells from their in vivo niche [11].

V. SOLUTION TOWARDS CHALLENGES OF ASC IN STEM CELL THERAPY

There are various methods in addressing the limitations of ASCs in stem cell therapy, namely finding

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optimal cell source for cell therapy, controlled-release exogeneous growth factors, preconditioning stem cells and finding optimal parameters for maximizing potential of ASCs such as routes of cell administration timing for cell therapy and number of cells for injection [10]. However, each method carries its own respective risks and requires more research on addressing their limitations. The latest discovery of stem cell research involved induced pluripotent stem cells (iPSCs) which sourced from reprogrammed somatic cells using different transcription factors (Oct4, Sox2, Klf4 and c-Myc). The steps to generate iPSCs are shown in Figure 2. There are two different methods to introduce the transcription or reprogramming factor; Integrating System which utilise retrovirus, lentivirus, and inducible lentivirus) and Non-Integrating Methods which based on non-integrating viral vectors, plasmid DNA transfer, transgene, recombinant proteins and synthetic mRNA. iPSCs currently remains a popular alternative in comparison with embryonic stem cells (ESCs) as iPSCs have similar pluripotency of ESCs while avoiding ethical issues concerning the depletion of embryos in research and clinics.

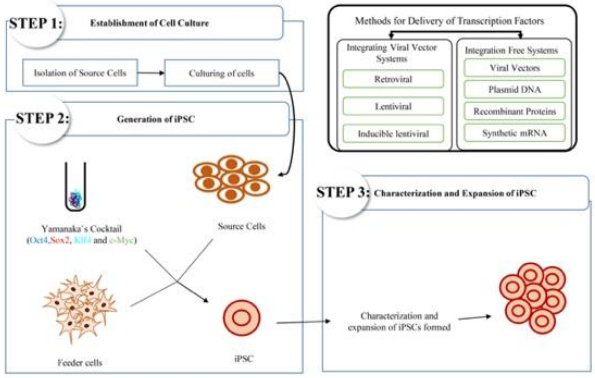

Figure 2: An overview of the methodology for the generation of iPSCs.

VI. APPLICATIONS OF ESC AND ASC

Currently, ESCs and ASCs are being used in various biology-based fields such as tissue engineering, regenerative medicine, disease modelling, drug discovery and cytotoxicity studies. The most commonly used source of ESC in stem cell therapy is human embryonic stem cells (hESCs). Among the variety of ASCs, iPSCs became a popular choice for stem cell research and therapy due to its properties similar to ESCs. Their benefits are shown in the following fields:

i. Disease Modelling

Disease modelling is one of the applications of ESC and ASC that have been used widely in order to determine cellular and molecular mechanisms of specific diseases and therapies improvement upon certain treatment [12]. Human embryonic stem cells from embryos with genetic diseases are helpful to understand the pathogenesis of diseases by modelling human diseases. A study has demonstrated that gene editing tools *in vitro* with Zinc finger (ZFN) and Transcription activator-like effector (TALEN) in hESC reproduced chromosomal translocation associated with Ewing sarcoma and anaplastic large cell lymphoma (ALCL). After thoroughly analyzing the genetic landscape present in tumor cells from patients with Ewing sarcoma, breakpoint junctions were recovered from hESCs. [13]. Another study showed that KCTD13 was knocked out in hESCs by using TALENs in order to mimic the Timothy syndrome, a type of an autism disorder which allows rapid drug screening. This study also resulted with the TS point mutation without genome modification at same loci [14].

The capability of self-renewing and able to differentiate into all types of cells of the human body makes iPSCs an ideal candidate for disease modelling as it can be used to mimic an in vivo microenvironment similar to human cell microenvironment. Furthermore, a patient specific iPSCs can be used for specific therapeutics treatment or drugs development. It can be used for identification of molecular networks that drive the different aspects related to pathogenesis in genetic-related syndromes such as Down's syndrome [15]. To achieve this, combination of iPSCs, microarray and RNA sequencing technology are used to generate phenotype-genotype maps of complex diseases by linking various defects with phenotype. Another disease that utilizes iPSCs for modelling is neurogenerative diseases such as Parkinson's Disease (PD). Under normal circumstances, treatment for PD had not been possible as neurons have already been lost by the time it manifested clinically, resulting in a high difficulty to study its underlying mechanisms for developing its treatment. Using iPSCs, studies were able to find out that a mutation in Leucine Rich Repeat Kinase 2 (LRRK2) gene was responsible for disruption in neuron survival, resulting in PD [16]. Based from on findings from modelling different diseases, iPSCs help in identifying the molecular mechanisms underlying the disease better which ultimately allows to know the disease better for the development of a treatment.

ii. Regenerative Medicine

Embryonic stem cells are known as one of the stem cells promises in regenerative medicine. It has been stated that ESC is able to give rise to more than 200 types of cells and used to treat various diseases due to its pluripotency nature. Studies have demonstrated that progenitors such as CD24+, CD49+ and CD133+ differentiate into pancreatic β-cells that secrete insulin by transplantation of ESCs-derived pancreatic progenitor cells. As a result, there were expressions of pancreatic β-cells markers including PDX1, INS1, GCK, and GLUT2 and improvement in glucose level to treat Type 1 and 2 diabetes [17,18]. Besides, another study has proved that human embryonic stem cells (hESC) are safe and effective therapy for spinal cord injury. This study

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resulted with regeneration of spinal tissue and development in balance, control and sensation that upon transplantation of ESCs to injury sites [19].

In regenerative medicine, damaged or degenerating tissues are restored by being created in a lab with the aid of iPSCs and then being transplanted to the damaged or degenerating area. These treatments provide a better result than using donated tissues or organs as these repaired iPSCs are created from the somatic cells from patient's own body hence, reducing the risk of immunodetection and fulfilling the scarcity of available tissue or organs. iPSCs can be used to treat accidental injuries, hematopoietic disorders, liver damage and creating various blood components ex vivo. By integrating gene therapy using iPSCs, symptoms caused by cells death via degenerative diseases can be treated such as Retinitis pigmentosa (RP) and Age-related Macular Degeneration (AMD) [20]. To create tissue for transplant or cure for degenerative diseases, normal iPSCs can be first created from normal cells or diseased cells which have to undergo corrections for its mutation. Illustration of reprogramming of somatic sells to an iPSCs by transcription factors is shown in Figure 3. The exact circumstances necessary for the growth of certain cell types are then provided to these normal iPSCs in order to differentiate them into other cell types. The organism from which the cells for the creation of iPSCs were extracted can then receive these restored cells by transplantation into its body.

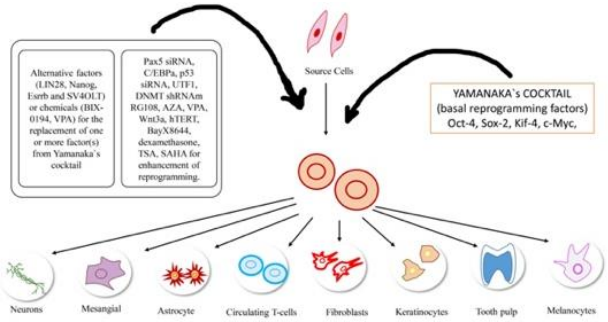

Figure 3: Introducing the four transcription factors causes somatic cells to be reprogrammed into iPSCs, which can then differentiate into several cell types.

iii. Drug Discovery and Cytotoxicity Studies

Currently, animals or in vitro animals derived cells are used as testing systems for drug discovery and toxicity. However, this system is limited by their inability to replicate the exact human physiological conditions and related phenotypic attribution while benefits demonstrated in the animal models sometimes do not exhibit similar characteristics in humans. Different animal models possess different tolerance and immunity, resulted them as a poor testing model for drug toxicity and carcinogenic agents [21]. Furthermore, In order for the effects of a newly discovered drug or therapy to be directly extrapolated to humans, it must first be tested on human cells or test models. A study revealed that 3D cell culture using organoids from retinal hESCs were performed for drug discovery and development. This study was cultured with serum floating EB-like aggregates from mESCs and ECM components [22]. Apart from using hESCs in drug discovery, iPSCs are also chosen as an alternative to animals' test subjects due to their ability to differentiate to all types of human body cells and displays of possible beneficial or side effects of testing newly discovered drugs will reflect upon various humans' body cells.

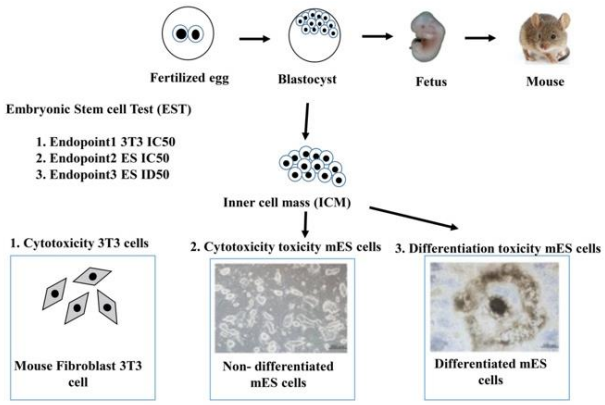

Figure 4: An overview of EST method.

Clinical trials will be much faster and cheaper to achieve result using iPSCs as models. Under the current system, each newly developed drug has to undergo intensive preclinical trials which incur high costs due to requirement of animal models for estimation of bioavailability of new drug. A significant amount medicine under development was abandoned due to lack of efficacy and concerns associated with safety. Moreover, a lack in early detection of drug toxicity in human tissues resulted in higher cost and extensive time consuming. By demonstrating cardiotoxicity or hepatotoxicity caused by the drugs before reaching clinical trials and thereby shortening the time taken to detect drugs that will fail due to cytotoxicity in the later stages of trials, the development of toxicity models that predict more accurately before clinical trials may help to reduce costs. Hence, embryonic stem cell test (EST) have been performed by using in vitro cytotoxicity test. For an example, mouse blastocyst-derived embryonic stem cell line D3 were used for cytotoxicity test with different ranges of test chemical concentrations [23]. A study reported that 78% of 20 reference compounds demonstrated matching toxicity by using toxic chemicals in cytotoxicity test [24]. Since iPSCs offer a more physiologically similar environment to that of humans than traditional testing systems, which use animals while providing toxicity details via various cytotoxicity assays, they offer a better alternative to conventional tests of toxicology and drug research and better chemical safety assessment [25]. It also enables identification of molecules therapeutically useful and able to modulate the behavior of tumorigenic and normal stem cells.

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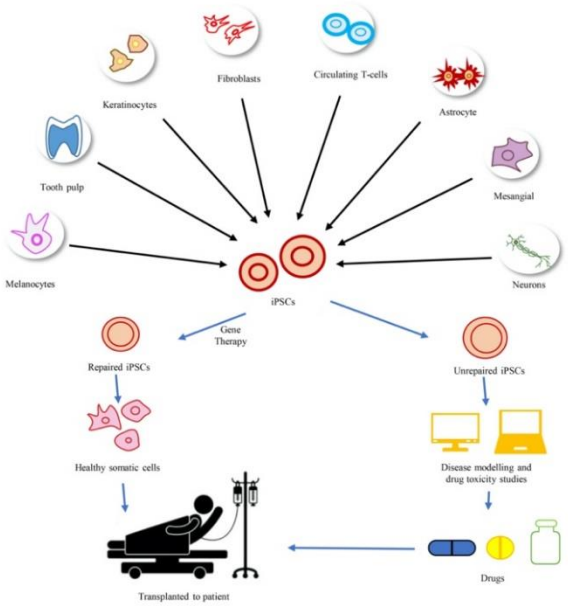

Figure 5: applications for iPSCs in the areas of drug development, disease modeling, and gene therapy.

VII. CONCLUSION

Stem cells have been used widely for therapies and research and also showed a great impact on understanding the cell biology, differentiation and development. Although ESC research provides opportunities for new therapies and scientific progressions, it raises critical ethical and policy issues. Hence, stem cell research must be conducted ethically while researchers must discuss the scientific problems to minimize these issues. ASC research has been playing important roles in therapies due to their availability and safety. This suggests that ASCs can be considered as a good option compared to ESC to use in stem cell therapy due to lack of ethical problems. ESC and iPSC are required to undergo further improvements in derivation and cultivation processes prior being applied in therapies. Further studies on innate regenerative and immunomodulatory characteristics of stem cells would be helpful to treat different diseases and injuries.

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