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A Review: Induced Pluripotent Stem Cells (iPS) Therapy Is the Best Method to Cure Non-Communicable Diseases Compared to Other Stem Cells ?

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ABSTRACT / ABSTRAK

Potensi sel punca dalam pengobatan atau terapi telah diketahui secara luas oleh karena sifat sel punca yang dapat berdiferensiasi menjadi suatu jenis sel tertentu dalam tubuh manusia. Aplikasi sel punca dalam pengobatan dan terapi adalah sebagai metode alternatif untuk menyembuhkan penyakit yang tidak dapat disembuhkan menggunakan obat-obatan kimia dan biologi, seperti Penyakit Tidak Menular . Pada umumnya, sel punca dapat dibagi menjadi tiga jenis, yaitu sel punca dewasa (Adult Stem Cells), sel punca embrionik manusia (Human Embryonic Stem Cells), dan sel induk pluripotent diinduksi (Induced Pluripotent Stem Cells/iPS). Masing-masing jenis sel punca memiliki keuntungan dan kerugian untuk penggunaannya dalam pengobatan dan terapi. Ulasan ilmiah ini bertujuan untuk menginvestigasi apakah sel induk pluripoten diinduksi (iPS) adalah pendekatan terbaik untuk menyembuhkan Penyakit Tidak Menular (PTM) dibandingkan dengan jenis sel punca yang lain. Selain itu, akan dibahas keterkaitan antara penelitian sel induk pluripotent di Indonesia dengan Peraturan Badan Pengawas Obat dan Makanan tentang Penilaian Sel Berbasis Manusia yang berlaku di Indonesia. Ulasan ini juga akan membahas adanya manfaat lain dari iPS dalam upaya pengobatan PTM. Hasil ulasan ini dapat digunakan untuk menambah pengetahuan bagi peneliti dan pelaku usaha tentang potensi terapi berbasil sel punca, khususnya jenis iPS, yang digunakan untuk mengobati PTM di Indonesia di masa depan. Bagi Badan Regulasi, ulasan ini dapat menjadi pertimbangan dalam menentukan kebijakan dan peraturan mengenai terapi berbasis sel punca, terutama terapi dari jenis iPS.

The potency of stem cells in treatment or therapy is widely known due the properties of stem cells to differentiate into a specialized cell type in a human body. Application of stem cells in medicine and therapy is mostly used for alternative treatment of diseases that could not be cured using chemicals or other biological drugs, such as Non-Communicable Diseases (NCDs). In general, stem cells are classified in three types, namely Adult Stem Cells (ASC), Human Embryonic Stem Cells (hESC), and Induced Pluripotent Stem Cells. Each type of the cells has advantages and drawbacks for application in medicine and therapy. This review investigates whether iPS is the best approach for non-communicable disease treatments among other stem cell types. In addition, it is going to be discussed the relationship between iPS products and the recent Regulation of Indonesian Food and Drug Authority

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(Indonesian FDA) about Human Based Cell Assessment. Further, it will be discussed about other potencies of iPS in NCDs treatment. Moreover, this scientific review may provide the new insights into stem cells based therapy for researchers and manufacturers particularly iPS for future NCD treatments in Indonesia. For the regulators, this review could be a consideration in determining policies and regulations regarding stem cell-based therapies.

Keywords: stem cells, non-communicable diseases, induced pluripotent stem cells
Kata Kunci: sel punca, penyakit tidak menular, sel induk pluripotent diinduksi

1. Introduction

Non-communicable diseases (NCDs) such as diabetes mellitus, cardiovascular diseases, cancer, and chronic lung disease have increased in recent years and caused 71% of all deaths (World Health Organization, 2020). In addition, the prevalence of NCDs and the mortality caused by NCDs in low-and-middle-income countries is higher than in high-income countries, thereby resulting the increasing of the global NCD burden (Ruby, et al., 2015, Jarvis et al., 2019). This condition is likely to challenge researchers and governments to find the effective treatments for NCDs. Most people with NCDs are treated by drug therapies, surgery, as well as counselling to prevent the diseases, such as heart attacks and strokes, to re-occur (Jarvis et al., 2019). Unfortunately, some aspects of these diseases cannot be treated using chemically synthesized drugs and surgery. Therefore, alternative treatments are needed to cure people with NCDs.

The properties of stem cells seem to be a promising alternative therapy to treat Non-Communicable Diseases (NCDs) patients. Stem cells are undifferentiated cells that can be induced to develop into numbers of different specialized cell types in the body with a more specific functions (Fossett and Khan, 2012; Weissman, 2000). One of their functions is a repair system for the body; hence, they possess the ability to renew themselves to repair and replace damaged tissues in the body. Besides, stem cells have two unique properties that make them different from other cells namely the capability to divide into new cells that remain a stem cell and the ability to become another specialized cell type (National Institutes of Health, 2016). Furthermore, stem cells have an ability to produce various cell types *in vitro*, which is important in cell-based therapies (Fossett and Khan, 2012). Thus, this makes stem cell therapies more interesting as preferred methods for the treatment of those diseases.

In general, there are three sources of stem cells which are Adult Stem Cells (ASC), Human Embryonic Stem Cells (hESC), as well as human Induced Pluripotent Stem Cells (iPS). ASC, also commonly known as somatic stem cells, are located in various tissues of the human body in a small percentage of cells, and surrounded by mature cells (Jones et al., 2002). While ASC are isolated from adult human body, hESC are derived from inner cell mass of human's embryos at the blastocyst stage (Shah, 2016). Compared to ASC and hESC, iPS is relatively new technology and the research related to this type of stem cells is developing. iPS is generated by reprogramming differentiated adult cells into embryonic-like stem cells (Pessôa, Bressan, Freude, 2019). iPS seems to have greater potential for the treatment of non-communicable diseases. This review aims to discuss whether iPS, compared to ASC and hESC, is the most promising method to cure non-communicable diseases. The argument is based on the comparison of the weakness, the strength, and the ethical debate of ASC, hESC, as well as iPS.

2. Adult Stem Cells

Adult stem Cells have been used in cell therapies to cure genetic disorders over decades. ASC was first studied by Friedenstein and colleagues by isolating adult mesenchymal stem cells from bone marrow (Jung, Bauer, Nolta, 2012). They reported that the cells are similar to fibroblasts which were able to replicate extensively in vitro (Fossett and Khan, 2012). Later, these cells were discovered to have adult stem cells characteristics since they are capable to differentiate into bone,

tendon, cartilage, and fat (Parekkadan and Milwid, 2010). Due to the ease of cell isolation from various adult tissues, such as bone marrow, umbilical cord, fat, and others, adult mesenchymal stem cells have been widely studied for medicine applications. Some therapies which use the cells are either through direct cell differentiation or indirectly through cytokine secretion or protein (Jung, Bauer, Nolta, 2012). Furthermore, the advantages of adult stem cell application are no ethical issue as well as the absence of self-rejection. Self-rejection occurs when the immune system recognizes the cells, the tissues, and the organs from other bodies. However, it seems that ASC have some limitations when treating many degenerative diseases.

Commonly, ASC are classified in two types which are autologous and allogenic. Autologous are stem cells isolated from patients and differentiated into particular cells or tissues, transplanted into the patients itself. In this case, the immune system of the patient may not recognize the transplant as parts of other bodies and self-rejection is unlikely to occur. For example, stem cells therapy to cure burnt skin, uses stem cells isolated from adipose tissue within the patient. Different from autologous, allogenic is stem cells isolated from donors and transplanted to recipients. Treatment using allogenic may induce immune-rejection from the recipients. Allogenic may be used for degenerative diseases treatment for elderly since the number of usable stem cells from young people is higher than older people due to the senescence of stem cells (Fossett and Khan, 2012). This senescence occurs because a particular protein is highly expressed in older people body which allows inducing cell death of somatic cells and stem cells (Mariano et al., 2015). Hence, if the number of stem cells of patients is low, donors of adult stem cells are needed. This also means treatment using ASC is likely to take a longer time since there is screening to find the most appropriate donor to minimize self-rejection from patient's body. Therefore, an alternative therapy is required to tackle this problem to reduce cost and time length of therapy.

Another weakness of ASC is that it is categorized as multipotent. Multipotent means the cells have limited ability to divide and differentiate into specific and specialized cells from the origin of the stem cells (Ghodsizad et al., 2010 cited in Kumar et al., 2012). For instance, stem cells that are isolated from blood (hematopoietic cells) can be induced into different blood cells types, but it cannot be induced into brain cells. Consequently, many degenerative disorders such as Parkinson's disease and amyotrophic lateral sclerosis (ALS), as well as neural injuries such as spinal cord injury cannot be treated by using adult stem cells because these types of cell are not easy to isolate and induce into other types of cell (Trounson & McDonald 2015). Thus, another method is needed to treat a great deal of non-communicable diseases.

3. Human Embryonic Stem Cells

The second approach of stem cells therapy currently used in some countries is Human Embryonic Stem Cells (hESC). It has great potential for producing adult stem cells due to their unlimited proliferation as well as differentiation capacity, but there are numerous drawbacks. hESC is pluripotent which means it can proliferate and differentiate into abundant types of cell in the body. Due to the characteristic of hESC, the cells have a greater potency to cure many non-communicable diseases. Nonetheless, some stem cells lines derived from hESC are unlikely to be safe for treatment due to the accumulation of mutations that may lead to tumor or cancer. This mutation appears to occur because of the instability of chromosome in prolonged embryonic stem cells in vitro (Moon et al. 2011). Furthermore, hESC transplantation may raise the chance of a rejection reaction since the donor cells and the recipient are immune incompatible. However, this problem could be overcome by therapeutic cloning. The method involves transferring the somatic nuclear cell from certain individuals into the egg cell then developing it into the pluripotent hESC (Medvedev, Shevchenko & Zakian 2010). Nevertheless, the efficiency of therapeutic cloning to harvest pluripotent cells is low (Medvedev, Shevchenko & Zakian 2010). In addition, this technology raises ethical concerns that

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are related to egg cell donation for research. In terms of the safety reasons of hESC, such as tumor potential and immune incompatibility, this method appears to face enormous difficulties in the future.

Stem cells therapy that is based on the Human Embryonic Stem Cells (hESC) seems to be difficult to apply due to controversial ethics. These ethical concerns are controversial and result in many governments not approving this research. The hESC is isolated from human embryos that are mostly taken from in vitro fertilization for research purposes (National Institutes of Health 2016). Some of the cells are also derived from frozen embryos that remain after couples undergo in vitro fertilization for infertility treatment. Ethical controversies are raised since the destruction of an embryo is an outcome in the process of making new tissues or organs. It is unquestionable that embryos continue to develop into fetus and baby if they are implanted into a woman's uterus. As a consequence, destroying an embryo is equivalent to killing a human. This is also supported by The President Council of Bioethics (cited in Lo & Parham 2009) who argues that religious and moral convictions believe that human life starts at conception and therefore, an embryo has human rights. Nevertheless, some countries, such as The USA and Canada have legalized the use of an embryo for stem cell research under deliberate scientific justification as well as the agreement from the couple who donate the embryo (National Institute of Health 2016, cited in Lo & Parham 2009). However, due to a great deal of controversial issues that surround hESC, a great deal of countries such as Indonesia, Ireland, France, and Italy have banned stem cells research that is based on hESC. The question is why countries spend considerable money for the hESC research while it still has many controversies and drawbacks regarding the safety of hESC, especially when an alternative method is available.

Besides the ethical debate, stem cells therapy that is based on hESC to treat human's degenerative diseases has faced considerable problems. Retinal pigmented epithelial cells (RPEs) can be made from 99 % pure of hESC. These RPEs seem to be successfully used to cure dry macular degeneration as well as Stargardt's macular dystrophy (Trounson & McDonald 2015). However, the patient that receive a transplant from hESC has to consume lifelong medicines to prevent from rejection reaction from the patient's immune system. In addition, the therapy that uses hESC still needs to consider some safety concerns, including immune rejection that is caused by non-autologous transplants, the possibility of harmful agents spreading from transplant to patient, the stem cell instability that may induce tumorigenic potential of transplanted cells (Hentze, Graichen & Colman 2006). Consequently, another source of stem cells is needed to cover the weaknesses of ASC and hESC, thereby science is looking at iPS.

4. Induced Pluripotent Stem Cells

Induced Pluripotent Stem cells (iPS) can be induced to differentiate into any human tissue and maybe used as a therapy for treating degenerative diseases. iPS is the cells that are isolated from adult cells then they are reprogrammed to have pluripotent characteristics. The characteristics of iPS apparently make the research more promising than that of adult stem cells. If cells are pluripotent, they can be induced into any types of cells, tissues, and organ in the body (Medvedev, Shevchenko & Zakian, 2010). Therefore, iPS can provide an unlimited supply of human tissues that are difficult to access for research and treatments. For instance, adult skin cells can be isolated; the gene inside is edited to become brain cells, kidney cells, and even heart cells. If any molecular defect in iPS can be corrected and the corrected iPS-derived tissue can be transplanted, this is likely to advance cell therapy in regenerative medicine. In addition, the transplant will not cause self-rejection because the source of iPS-derived tissue is isolated from the patient itself. Hence, iPS is the best solution to cover the weaknesses of ASC and hESC.

Despite the enormous potential of iPS for personalized therapy of non-communicable diseases, there are some challenges related to iPS production and the safety of iPS in cell replacement therapy. Firstly, the gene set that is used for developing iPS is associated with the development of

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multiple tumors, known as oncogenetic. Secondly, a retrovirus is used for vectors that deliver the gene set into adult somatic cells since the efficiency of the gene transferring is quite high. The detrimental side of the process is the DNA integration of virus into the host cell genome and may cause mutagenesis. As a consequence, some scientists continue to develop stem cells that are based on human embryonic stem cells. In addition, pro-hESC scientists consider that cells that are derived from iPS have different characteristics to the origin cells. Nonetheless, there are some new methods to generate iPS, namely using another gene set that does not cause tumors and to replace the use of retrovirus (Higgs, 2008). Furthermore, iPS has successfully cured sickle cell anemia in humanized mice; also the cells from iPS has not found to develop into a tumor, based on the experiment (Hanna et al., cited in Higgs, 2008). Another iPS research by Wernig et al. (2008) showed that iPS engineered from mice fibroblast could differentiate into neural and glial cells which then cured Parkinson-mice mode. Although iPS based therapy may pose some challenges, more studies showed the success pre-clinical trials of iPS therapy in animals.

After successful iPS research using animals, there are some clinical trials in human. One significant step of iPS therapy is the success of human clinical trial for the treatment of age-related macular degeneration (AMD) of a Japanese woman in 2014. AMD is one of the retinal degenerative diseases which can cause the irreversible vision loss due to dysfunction of the retinal pigment epithelium (RPE), cells layer that supports photoreceptors needed for vision (Song & Bharti 2016). Starting from the isolation of the patient's skin, the skin cells are reprogrammed to produce iPS then these cells were developed to differentiate into retinal pigment epithelium cells and grow into a sheet for implantation. Another iPS clinical trial in human was iPS cells generated from skin fibroblast cells of 82 year old woman suffered from amyotrophic lateral sclerosis (ALS). The cells were differentiated into motoric neuron cells, which are the damaged cells in ALS patients (Dimos et al., 2008). With these meaningful human trials, it seems that iPS is a very promising method of genetic diseases treatment.

Despite the success of iPS therapy in human, this iPS-based therapy is very costly because iPS is a starting material which must undergo long and different manufacturing processes. Furthermore, the clinical studies of each new patient-specific product from iPS must be tested both pre-clinic and clinic, as well as be approved by authorized institution. Therefore, these series of production and studies of iPS-transplants will make the cost very prohibitive. Nevertheless, there are some strategies which are likely to reduce the cost of iPS product. One of the solutions is to simplify the procedures to operate rules and patent licensing. Another solution, there must be any harmonization of international standards which are considered of general approval (Rao & Atala 2016). Additionally, these alternative solutions to reduce the cost of iPS therapy still need cooperation with all stakeholders in order to ensure final approval. Moreover, with the increasing of molecular biology technology, it is predicted that the cost of iPS therapy will be cheaper since the processes of making iPS can be reduced.

Since iPS-based therapy is very promising, the safety, the quality, and the efficacy of iPS must be ensured. Based on the US Food and Drug Administration (FDA) that the final cellular products injected into a patient must meet some criteria, such as identity, potency, purity, as well as clinical safety (Jung, Bauer, Nolta, 2012). In addition to Regulation of US FDA, Indonesia has a regulation which controls and assures the safety, the quality, and the efficacy of stem cell products, including iPSc. Based on Regulation of Indonesian FDA number 18 year 2020, stem cell production shall meet GMP (Good Manufacturing Practice) which is proven by GMP certificates and other equal certificates (Peraturan Badan Pengawas Obat dan Makanan No. 18 tahun 2020). In order to minimize the risk of iPS products, it shall be ensured that the raw materials are free from Transmissible Spongiform Encephalopathies (TSE) or prion protein. However, it was demonstrated that prion protein has some roles in stem cell differentiation (Martelluci et al., 2020). Nevertheless, prion protein is able to cause adverse effects on human's health; hence, prion protein contamination in stem cell products shall be avoided. Characterisation of iPS products shall be carried out to ensure

the properties of modified cells. Besides, final products of iPS are required to meet some particular concerns for stem cells, such as sterility, freedom from endotoxin, viability, in vitro and in vivo potency, as well as tumorigenicity. These all requirements shall be met by iPS products and evaluated by Indonesian FDA before the products are released and used by the patients.

To date, not many publications about iPS can be found in Indonesia. It is likely that a few Indonesian researchers have studied the potency of iPS (Zainuri, 2014). Since the percentage of NCDs has been higher over few past years, alternative methods of NCD treatments, such as iPS-based therapy, should be studied thoroughly. Furthermore, circumcision culture in Indonesia may provide cheap and sustained cell source for studying iPS. The circumcision skin may be reprogrammed into specific mature somatic cells (Zainuri, 2014). Moreover, transduction and transfection are biotechnological techniques which are mastered by some Indonesian researchers (Zainuri, 2014). This skill may enable gene insertion in generation of iPS. Therefore, considering these aspects, it is possible that iPS could be developed in Indonesia.

Another use of iPS is that it is often used for in vitro modeling human diseases, screening drug, and studying toxicology (Colman & Dreesen, cited in Yee 2010). This method arises because the somatic cells that are derived from iPS still demonstrate the characteristics of regenerative disease from the origin of the cells. For instance, if iPS-red blood cells are constructed from patient's skin cells that have Parkinson's disease, the iPS-neuron cells will exhibit the same phenotype as the brain of Parkinson's disease's patient. By using this approach, researchers can undergo studies to find the most suitable drug or therapy that is needed. Unlike the cost of iPS transplantation, which is very expensive, drug screening that is based on iPS might relatively cheaper since it does not require lengthy processes for final approval of post-market studies. Thus, this is likely to make iPS - based therapy is viable for degenerative diseases treatments worldwide.

5. Conclusion

In conclusion, iPS – based therapy certainly offers greater potential compared to ASC and hESC. Some obvious benefits of iPS are it is pluripotent, relatively easier to be isolated, as well as it cannot cause immune rejection. Besides, it does not have controversies and numerous concerns from bioethical organizations and religions around the world. Despite greater advantages of iPS, some drawbacks of iPS, such as oncological risks, must be overcome. Although iPS still needs further research in order to iPS treatment is available, iPS can be developed into tissues in order to screen the suitable drug therapies for patients who suffer NCDs. The improvement of iPS manufacture in the future will make iPS – therapy is accessible and affordable for every people who suffers NCDs. Since Indonesian FDA has issued the regulation about stem cell products and iPS has great potency in NCDs treatments, it is a considerable opportunity for researchers and manufactures to study as well as to develop iPS-based products.

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