Perspective Article

Should the US Government Fund Human Embryonic Stem Cell Research?

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Abstract: Human embryonic stem (ES) cells isolated from human embryos are pluripotent and they have the remarkable ability to differentiate into all different cell types in the human body, thus holding enormous potential for therapeutic applications. But the use of human ES cells has been a topic of ethical and legal debate as it involves the destruction of human embryos. In addition, Immune rejection is another major concern when using human ES cells or their derived other cells as therapies in transplantation. The breakthrough in stem cell research came when human induced pluripotent stem cells (iPSCs) were discovered in 2007. Human iPSCs, like ES cells, have the potential to differentiate into all cell types in the human body, but don't involve any human embryos. In addition, it is generally believed that human iPS cells reprogrammed from a patient's own somatic cells would reduce the risk of immune rejection when they or their-derived cells are transplanted back to the same patient. Since the discovery of human iPS cells, a question remains whether the US Government continues to fund human ES cell research. In this article, I discuss this question from three perspectives, the cell originating sources and immunogenicity, clinical trial results and safety for disease treatments.

Keywords: iPS cells, ES cells, degenerative diseases, immune rejection, cell therapy.

Introduction

Human ES cells are pluripotent stem cells derived from the inner cell mass of a developing human embryo at the blastocyst stage, which is about 5-7 days after fertilization. Human ES cells are pluripotent, and they can self-replicate indefinitely as well as differentiate into all the different cell types in the human body including neurons, muscle cells, blood cells, and many others [1]. Therefore, human ES cells offer a great hope to treat many major diseases such as cardiac failure, neurodegenerative diseases, and diabetes. According to the World health Organization, approximately 17.9 million people die from cardiovascular disease each year and 8.5% of adults have diabetes in the world [2, 3]. In addition, Kramarow and Tejada-Vera from the Centers for Disease Control and Prevention reported that dementia took 261,914 deaths in 2017 in USA alone [4]. Therefore, the world is currently facing multiple urgent health challenges, which may be overcome by human ES cells-based regenerative medicine.

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In the past, National Institutes of Health (NIH) has invested significantly in human ES cell research that uses the existing human ES cell lines approved by NIH. For instance, in the 2009 fiscal year, NIH funded more than $20 million to human ES cell research [5]. Nevertheless, the use of human embryonic stem cells has been a topic of ethical and legal debate, as it involves the destruction of human embryos.

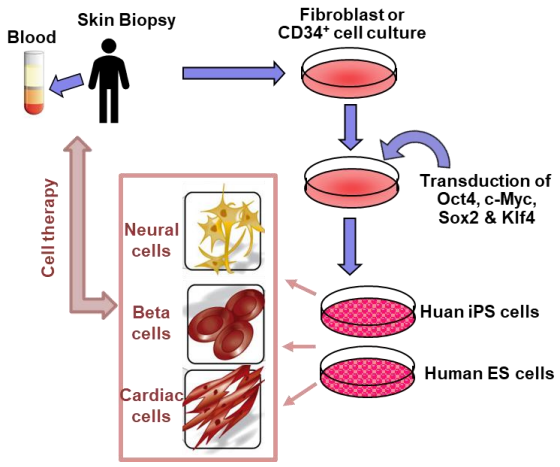

Figure 1. Fibroblast cells isolated from human skin biopsy or blood cells can be reprogrammed into human iPS cells by using four transcription factors (Oct4, c-Myc, Sox2 and Klf4). The human iPS cells, like human ES cells, be differentiated into various types of cells which could be used as cell therapy for disease treatment.

The research interest in human ES cells was slightly tamped down with the advent of induced pluripotent stem (iPS) cells. Human iPS cells were a new type of human stem cells that were reprogrammed from human skin cells with the four transcription factors by Dr. Yamanaka and his colleagues [6] (**Figure 1**). Similar to human ES cells, human iPS cells are capable of unlimited self-replication and differentiation into all body cell types [7]. Given the similar features of human iPS cells to human ES cells but without requirement of killing embryo like human ES cells, it seems that human iPS cells could outperform and replace human ES cells. This leads to a new question: should the US government continue to fund research of human ES cells. One way to address this question is to understand scientific perspectives in both human ES cell and iPS cell research. Learning different scientific perspectives on this issue will greatly help better decisions, which will ultimately benefit all patients suffering from major diseases.

From Perspective of Cell Originating Sources and Immunogenicity

In terms of cell originating sources and immunogenicity, it has been widely agreed that human iPS cells seem to have more advantages over human ES cells. Human ES cells are routinely isolated from the inner cell mass of blastocyst which necessitates embryo destruction. In contrast, human iPS cells can be reprogrammed from human body cells such as skin cells and blood cells, and they display capacity of self-replication and differentiation like human ES cells [7]. In addition, human iPS cells can be programmed from a patient and the iPS cell-derived cells be transplanted back to the same patient, therefore, clinical application of human iPS cells could minimize the immune reaction. Whereas most researchers think that transplanting human ES cells to a patient can potentially cause immune rejection as patient immune system recognizes that human ES-derived cells are not from its own body and thus attacks those cells [7]. However, this traditional view was challenged by Li and his colleagues from Krembil Centre for Stem Cell Biology and Regenerative Medicine in Canada [8]. They found that human ES cells possess immune-privileged properties which makes immune rejection of human ES cells less of a concern in therapeutic uses (8). In addition, Robertson et al showed that ES cell-derived tissues display inherent immune privilege that promotes the induction of immune tolerance in a mouse model [9]. In summary, human iPS cells are generally preferred over human ES cells in term of their cell originating sources and immunogenicity though the opposing viewpoint does exist.

From Perspective of Clinical Trial Results

From clinical trial result point of view, it appears that human ES cells demonstrated more advantages over human iPS cells. Several successes in human ES-based clinical trials have been reported whereas no human iPS cells-based clinical trials have been accomplished yet. For instance, macular degeneration has been a target disease for human ES-cell therapies. In 2018, research led by ophthalmologist Pete Coffey, director of the London Project to Cure Blindness and the University of California, Santa Barbara, reported that they implanted cells made from human ES cells into the damaged retinas of two patients, and the participants regained the ability to read year after one year treatment [10]. It is a "big step forward" for the field as said by Alan Marmorstein, an ophthalmologist at Mayo Clinic in Rochester, Minnesota [10]. In October 2021, it was reported that a breakthrough treatment of Type 1 diabetes was made in a clinical trial led by Dr. Doug Melton, co-director of Harvard Stem Cell Institute and Vertex Pharmaceuticals [11]. They first fully differentiated human ES cells into pancreatic islet cells named VX-880, and then infused VX-800 into a patient of Type 1 diabetes with immunosuppressive therapy together. Their result showed that human ES cell-derived VX-800 robustly restored the patient islet cell function on Day 90 in its Phase 1/2 clinical trial [11]. "This success potentially obviates the lifelong need for patients with diabetes to self-inject insulin as the replacement cells provide the patient with the natural factory to make their own insulin," said Dr. Melton [11]. In contrast to successes of human ES cells in clinical trials, no achievement of human iPS cells for disease treatment have been reported yet. The first human clinical trial using cells derived from human iPS cells has been led by ophthalmologist Masayo Takahashi at the RIKEN Center for Developmental Biology to treat macular degeneration. But it was halted in 2014 for procedure modification and restarted in 2017, and again stopped in 2018 when a membrane unexpectedly developed in a participant eye [10]. Despite of current unsuccess of human iPS cells in clinical trials, many scientists argue that human iPS cells will eventually win out over human ES cells as iPS cells can derive cells and tissues of the same patient which won't cause any immune reaction when transplanted [12].

From Prospective of Safety for Disease Treatments

From the safety perspective for disease treatment, many scientists believe human ES cells are relatively safer for clinical application than human iPS cells. Human iPS cells are reprogrammed from human body cells with the introduction of four transcription factors.

These four transcription factors are largely delivered into body cells using retroviruses, but retroviruses can randomly insert transcription factor DNAs anywhere into the human genome which may trigger cancer-causing gene expression [12, 13]. Therefore, using human iPS cells generated by retroviruses to treat diseases may cause cancer in patients. However, others argue that this problem can be solved by using new methods for iPS cell reprogramming. For instance, some researchers have developed new ways by using small molecules and growth factors to replace retroviruses for human iPS cells reprogramming [13], which make human iPS cells safer for clinical usage. But some researchers believe that human iPS cells still have epigenetic issues and their epigenetic memory could influence the human iPS cells transplantation outcomes and safety [14].

Conclusion

Despite all these different perspectives in human ES cells and iPS cells, the significance of human ES cells should not be compromised by the iPS cells. Dr. Yamanaka, the Nobel laureate in medicine 2012 for his contribution to iPS cells, said "the importance of human ES cells is no less now than 20 years ago, and I do not imagine it will be any lower in the future" [10]. Thus, it may be a wise decision that the US government continue investing more in human ES cells. Given their unique capacity, human ES cells have emerged as an important research field.

Conclusion

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References

1. Vazin T, Freed WJ. (2010). Human embryonic stem cells: derivation, culture, and differentiation: a review. Restorative Neurology and Neuroscience.28(4):589-603.
2. World Health Organization, Cardiovascular diseases (2021). https://www.who.int/health-topics/cardiovascular-diseases#tab=tab_1 (accessed on 2023-05-24)
3. World Health Organization, Diabetes (2021). https://www.who.int/news-room/fact-sheets/detail/diabetes (accessed on 2023-06-12)
4. Kramarow EA, Tejada-Vera B. (2019). Dementia Mortality in the United States, 2000-2017. National Vital Statistics Reports. 68(2):1-29.
5. First Human Embryonic Stem Cell Lines Approved for Use Under New NIH Guidelines (2009) https://www.nih.gov/news-events/news-releases/first-human-embryonic-stem-cell-lines-approved-use-under-new-nih-guidelines (accessed on 2023-06-20)
6. Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, et al. (2007) Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell.;131(5):861-72.
7. Kolios G, Moodley Y. (2013). Introduction to stem cells and regenerative medicine. Respiration. 85(1):3-10.
8. Li L, Baroja ML, Majumdar A, Chadwick K, Rouleau A, Gallacher L, et al. (2004). Human embryonic stem cells possess immune-privileged properties. Stem Cells. 22(4):448-56.
9. Robertson NJ, Brook FA, Gardner RL, Cobbold SP, Waldmann H, Fairchild PJ. Embryonic stem cell-derived tissues are immunogenic but their inherent immune privilege promotes the induction of tolerance. Proc Natl Acad Sci U S A. 2007 Dec 26;104(52):20920-5.
10. da Cruz L, Fynes K, Georgiadis O, Kerby J, Luo YH, Ahmado A, et al. (2018). Phase 1 clinical study of an embryonic stem cell-derived retinal pigment epithelium patch in age-related macular degeneration. Nat Biotechnol. 36(4):328-37.
11. A new therapy for treating Type 1 diabetes (2021). https://hsci.harvard.edu/news/new-therapy-treating-type-1-diabetes
12. Cyranoski D. (2018). The cells that sparked a revolution. Nature. 555(7697):428-30.
13. Kim Y, Jeong J, Choi D. (2020). Small-molecule-mediated reprogramming: a silver lining for regenerative medicine. Exp Mol Med. 52(2):213-26.
14. Scesa G, Adami R, Bottai D. (2021). iPSC Preparation and Epigenetic Memory: Does the Tissue Origin Matter? Cells-Basel.10(6).