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ORIGINAL PAPER

Some Ethical Concerns About Human Induced Pluripotent Stem Cells

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Abstract Human induced pluripotent stem cells can be obtained from somatic cells, and their derivation does not require destruction of embryos, thus avoiding ethical problems arising from the destruction of human embryos. This type of stem cell may provide an important tool for stem cell therapy, but it also results in some ethical concerns. It is likely that abnormal reprogramming occurs in the induction of human induced pluripotent stem cells, and that the stem cells generate tumors in the process of stem cell therapy. Human induced pluripotent stem cells should not be used to clone human beings, to produce human germ cells, nor to make human embryos. Informed consent should be obtained from patients in stem cell therapy.

Keywords Ethical concerns · Human induced pluripotent stem cells · Reprogramming · Tumorigenicity · Human cloning · Human germ cell · Human embryo · Informed consent

Introduction

Bioethical debates about human embryonic stem cells have continued for many years, and the main reason for the debates is because harvest of human embryonic stem cells requires destruction of the embryos. Takahashi reported that mouse somatic cells can be reprogrammed into induced pluripotent stem cells that have properties of embryonic stem cells and express embryonic stem cell marker genes (Takahashi and Yamanaka 2006). In recent years, human somatic cells can also be induced to become pluripotent stem cells (Maherali et al. 2008; Soldner et al. 2009, 2011; Churko et al. 2013). Derivation of human induced pluripotent stem cells (hiPSCs) from somatic cells can avoid destruction of human embryos and thus

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bypass ethical problems arising from the destruction of embryos. Because production of this type of stem cell does not require destruction of human embryos, and somatic cells used as biomaterials for derivation of hiPSCs are easily available, techniques of hiPSCs induction can be manipulated in many laboratories in the world. Scientists think that hiPSCs can differentiate into specific cell types transplanted into patients to replace and repair the damaged or diseased tissues of the patients. Although use of hiPSCs are likely to achieve the purpose of treating diseases and have attractive prospects for cell therapy, there are still some ethical concerns surrounding hiPSCs, including abnormal reprogramming, tumorigenicity, cloning human beings, producing human germ cells, making human embryos and informed consent.

Abnormal Reprogramming in the Process of hiPSCs Induction

Although hiPSCs are derived from human somatic cells, their epigenetic profiling is different from that of somatic cells. hiPSCs have the same genetic material as somatic cells, so immune rejection is reduced after hiPSCs are used to repair the diseased tissues and organs of the patients in stem cell therapy. This potential of hiPSCs has caught great attention of scientists. hiPSCs are generated from reprogrammed somatic cells, but many mechanisms of reprogramming are still unknown. This would raise ethical concerns about the process of somatic cell reprogramming. Induction of hiPSCs still faces many technical challenges during the reprogramming process. Induced pluripotent stem cells show aberrant reprogramming of DNA methylation (Lister et al. 2011) and are different with regards to gene expression (Okita et al. 2007). Reprogramming process is associated with deletions of tumor-suppressor genes (Laurent et al. 2011). Abnormal hiPSCs are regarded as defective and can not be used for cell replacement therapy. In addition, the generated hiPSCs can be genetically modified, so alterations in gene expression will happen in the cells and are likely to affect the abilities of differentiation, proliferation and development of hiPSCs. Further studies are needed to know whether hiPSCs are identical to human embryonic stem cells in terms of biological characteristics. Reprogramming techniques of somatic cells should be improved, and tests for safety of hiPSCs should be conducted before hiPSCs are used in cell therapy.

Tumorigenicity in Cell Therapy of hiPSCs

Researchers can reprogram somatic cells to obtain induced pluripotent stem cells. This type of stem cell may be a powerful tool in regenerative medicine, but its potential tumorigenicity is a significant challenge for the clinical use (Chen et al. 2014). Aneuploidy may increase the tumorigenicity of hiPSCs (Mayshar et al. 2010). hiPSCs are supposed to be applied in transplantation therapy for the purpose of treating some intractable diseases. If hiPSCs transformed into malignant cells are transplanted into patients in therapeutic applications, the health of the patients will

be threatened. This problem would raise widespread ethical concerns about safety of hiPSCs in the applications.

hiPSCs are capable of unlimited proliferation and can be induced to differentiate into other types of cells having potentiality to treat some diseases after transplantation. It is important that the transplanted cells maintain normal growth and development in proper position and perform normal functions in vivo. If differentiated cells transplanted into the body result in uncontrolled cell proliferation and generate tumor at the sites of implantation, serious ethical problems arise. Applications of hiPSCs will raise many challenges in transplantation therapy. It is important to keep the stability of the genetic and epigenetic characteristics of the stem cells in the process of culturing, proliferating and differentiating of hiPSCs. How to recognize and eliminate cancer cells during the induction and differentiation of hiPSCs? How to make hiPSCs differentiate into specific cell types and deliver the differentiated cells to the body safely and effectively? Intensive studies of hiPSCs should be needed before they could be extensively used for cell therapy.

Cloning Human Beings Using hiPSCs

Somatic cells can be induced into pluripotent stem cells, and the stem cells need to be tested strictly to see if they have the characteristics of embryonic stem cells before applications of them. Can the induced cells express pluripotency markers? Whether the cells have high abilities of regeneration and differentiation? At present, tetraploid complementation is a strict method of testing pluripotency of induced pluripotent stem cells. This method is performed by injecting of the stem cells into tetraploid embryos to obtain reconstructed embryos that are then transferred into recipients to see if the reconstructed embryos have the ability to develop into fetuses. Tetraploid embryos are composed of tetraploid cells, and they can't develop into fetus. The reconstructed embryos from induced pluripotent stem cells and tetraploid embryos can develop into fetuses, suggesting that the stem cells have the capacity to form new lives. Mice have been obtained from induced pluripotent stem cells using the tetraploid complementation method (Zhao et al. 2009, 2010; Kang et al. 2009; Boland et al. 2009). Scientists believe that this type of stem cell acquires pluripotency in the process of somatic cell reprogramming.

hiPSCs have the characteristic of pluripotent cells and can be used as a source of stem cells for transplantation therapy. This discovery brings excitement to scientists. In addition, unlike embryonic stem cells that are derived from destructed embryos, hiPSCs can be obtained from somatic cells by a means of reprogramming without destruction of embryos. This would avoid ethical problems associated with the destruction of human embryos for acquiring stem cells. With the birth of cloned animal, human cloning has been an area of ethical debate. If people who have lost their ability of reproduction want to have babies that are genetically related to them, they are likely to adopt the methods of hiPSCs induction and tetraploid complementation to obtain offspring derived from their skin cells or other kinds of somatic cells. These offspring are genetically equivalent to the somatic cell donor, that is, the offspring are the clones of the cell donor. Scientists have

succeeded in producing animal clones from induced pluripotent stem cells, indicating that human cloning from hiPSCs may be technically possible. But human cloning is ethically objectionable, it is necessary to formulate corresponding regulation to explicitly ban human cloning created by hiPSCs technique and other techniques.

In nuclear transfer cloning, somatic cell nuclei need to be transferred into enucleated oocytes to reconstruct embryos, so oocytes are destructed in the procedure of cloning. One may think that human cloning using the methods of hiPSCs induction and tetraploid complementation does not require destruction of human oocytes, and therefore may be ethically less controversial than the nuclear transfer cloning. However, human tetraploid embryos need to be provided in the method of tetraploid complementation, and they can be obtained through fusion of cells from human diploid embryos, so normal diploid embryos are destroyed. This would lead to serious ethical problems. Human oocytes are just germ cells, and they can not develop into offspring until they are fertilized, but human diploid embryos have the potential to form fetuses under normal circumstances. So cloning human beings using hiPSCs may be more ethically problematic than cloning human beings by nuclear transfer technique. In the tetraploid complementation method, new human embryos are obtained by reconstruction of hiPSCs and tetraploid embryos, but they may assume low viability when compared to artificial fertilization embryos and natural fertilization embryos. So a large number of human reconstructed embryos will likely be produced in order to improve the birth rate of cloned offspring. A lot of diploid human embryos are likely to be destroyed to generate tetraploid embryos used in the process of tetraploid complementation. This may be equivalent to sacrificing many people's normal life for a person's life. In addition, if hiPSCs are genetically modified and then used for cloning in order to obtain offspring with specific characteristics, the cloned person is likely to be treated as a pure tool of genetic modification. This may result in serious ethical problems. Due to technical limitations, expected characteristics of the cloned human may fail to occur. In contrast, it is possible that some defective characteristics are seen in the cloned offspring, and the characteristics are carried into next generation. These results will have a negative impact on the cloned person and their descendants.

Producing Germ Cells from hiPSCs

After the discovery of induced pluripotent stem cells, scientists believe that the stem cells can differentiate into germ cells used for artificial reproduction. Mouse primordial germ cell-like cells can be generated from induced pluripotent stem cells (Hayashi et al. 2011). Oocytes from mouse primordial germ cell-like cells have the ability to mature and fertilize in vitro, and offspring can be obtained (Hayashi et al. 2012; Hayashi and Saitou 2013). It may be possible to obtain human germ cells from hiPSCs. With development of hiPSCs induction and differentiation techniques, people may use germ cells derived from hiPSCs to produce offspring because of alluring prospect of the techniques. Some individuals, whether they are young or old, fertile or infertile, are likely to agree that their somatic cells are used as donor

cells to be induced into hiPSCs subsequently differentiated into germ cells such as sperm and oocytes. It is possible that the germ cells from hiPSCs are used for fertilization, and the fertilized oocytes are transplanted into uterus to produce offspring. Therefore, by differentiating of hiPSCs into germ cells, many people will likely become parents. This could meet the demands of infertile couples and gay couples who want to have genetically related children. In addition, it may be that genetic modification is introduced to the artificial germ cells derived from hiPSCs, and particular types of germ cells are selected for reproduction so as to obtain progeny with desired phenotypic traits.

Although reproductive technique using germ cells from hiPSCs is very alluring, it carries ethical problems. Techniques of artificial germ cell induction from hiPSCs and reproduction using the germ cells are still in the early stage of development, and many technical problems need to be solved. Some key issues are whether artificial germ cells from hiPSCs have the same cell morphology and structures as natural germ cells, whether the artificial germ cells can maintain genetic stability without abnormalities of chromosomes and genetic mutation, whether the artificial germ cells have the same ability of fertilization as normal germ cells, and whether embryo produced from artificial germ cells have the same developmental potentiality as embryos derived from natural germ cells. It is likely that abnormal chromosomes and mutant genes occur in artificial germ cells generated from hiPSCs and in embryos from the artificial germ cells. This abnormality could lead to serious ethical problems. In order to improve the success rates of the research, a large number of artificial germ cells will likely be produced, and they may be subsequently used for fertilization to generate many human embryos. High quality embryos may be selected for transplantation, while poor quality embryos are likely to be destroyed or discarded. This will raise ethical concerns regarding destruction of human embryos. For those who believe that human embryos have the same moral status as persons, destruction of embryos is unethical and will cause serious ethical problems. In addition, in order to generate offspring with specific phenotypic traits, genetic modifications are introduced to the artificial germ cells from hiPSCs, and the designed offspring would be treated as a tool to meet specific purposes of people whose somatic cells are used for production of hiPSCs. Artificial design has a bad influence on the physical and psychological development of offspring from hiPSCs, and this will raise ethical concerns about the reproductive technique using germ cells from hiPSCs.

Informed Consent in the Applications of hiPSCs

Somatic cells of patients can be reprogrammed into hiPSCs under appropriate conditions. Before hiPSCs research is performed, informed consent should be obtained from somatic cell donor. Informed consent is a major ethical concern in derivation and applications of hiPSCs, and hiPSCs can be induced from somatic cells only if cell donors agree to take the cells from their bodies for derivation of hiPSCs. Cell donors in hiPSCs research have rights to know body parts from which their cells will be taken, the methods applied to derive the body cells, and the areas

of hiPSCs research involving use of the donated cells. In addition, in order to study properties of hiPSCs obtained from somatic cells and properties of differentiated cells derived from the hiPSCs, scientists are likely to carry out a series of experimental studies of hiPSCs, so informed consent should also be obtained from the donors in the studies. Whether donated cells will be used for experimental studies associated with hiPSCs research? Whether the donated cells and the derived hiPSCs will be used to develop models and products for diagnose and therapy of diseases? Cell donors should also know whether they may be harmed during donation of their body cells, what harm may occur in this procedure, and how they will be treated in case of damage to their bodies. It is very important to obtain informed consent of patients in applications of hiPSCs. Informed consent will not only protect the rights and interests of patients and display respect for them, but also let the patients know that risks and uncertainties are likely to exist in the process of cell therapy using hiPSCs. Patients should recognize the status of their diseases and the importance of therapy. They should also know why hiPSCs therapy is taken to treat their diseases, what the efficiency of hiPSCs therapy is at present, and whether they agree to accept the consequences of ineffective treatment and damage to their bodies in the course of therapy.

It may be difficult to obtain informed consent in hiPSCs research and therapy. Patients should understand informed consent, so they will enjoy the success of treatment, such as recovery of body health, rescue and extension of life. But they also bear risk or even fatal consequences of treatment physically and spiritually if hiPSCs therapy fails. The ethical committee consisting of ethicists, legal experts, doctors and biologists needs to be established, and informed consent of hiPSCs therapy will be examined and approved by the committee. Informed consent of hiPSCs therapy should not violate the ethical and legal regulations, and this requires efforts of ethicists and legal experts. It may be a difficult thing to persuade patients to donate their cells for hiPSCs research and therapy. Many patients are the common people of our society and may not know much biological and medical knowledge involved in the hiPSCs therapy. Given limited understanding of hiPSCs knowledge, patients will likely doubt that stem cell therapy using hiPSCs is unsafe, and this could place restrictions on informed consent of patients. In order to enable patients to better understand hiPSCs therapy, doctors and biological experts should explain some knowledge involved in the hiPSCs therapy. Many studies of human stem cell therapy are in the initial stage, and their success rates of clinical applications are still very low, thus limiting informed consent from patients. hiPSCs therapy is a new field of disease treatment. Due to limitations of technical development, specific cell types that patient bodies need in hiPSCs therapy may fail to be produced, the specific cells from hiPSCs may fail to exercise right functions, and hiPSCs may transform into malignant cells causing cancer or other diseases in the therapy. All these possibilities would lead to treatment failure, and patients should decide whether they are willing to bear the treatment results.

Informed consent should be obtained from patients who want to treat diseases through hiPSCs therapy. If patients have known and agree with informed consent, they can sign the informed consent form. It is possible that some patients with brain damage have impaired cognitive capacity, thereby limiting their ability of informed

consent. In this case, their empowered relatives can decide whether to sign the informed consent form if they have known and agree with informed consent of hiPSCs therapy. These efforts may provide a valuable opportunity to restore health or to save lives of the patients.

Conclusion

In conclusion, hiPSCs can be induced from somatic cells, and then be differentiated into specific cell types that patients needs. Studies on hiPSCs offer new opportunities for medical treatment, but they also face many challenges. The challenges include improving techniques of hiPSCs induction and differentiation and resolving ethical concerns related to applications of hiPSCs. Further studies are needed to learn how to maintain genetic stability in the process of somatic cell reprogramming, and how to avoid tumorigenicity of hiPSCs. hiPSCs can be differentiated into a variety of cell types applied to replacement therapy, and it is important to improve differentiation efficiency of hiPSCs and to find safe and effective methods of transplanting cells into patients in cell therapy. Human cloning is unethical, it should be prohibited to use hiPSCs to clone human being. Human embryos have a special moral status, so hiPSCs should not be used for creation of human embryos. Applications of hiPSCs provide an important way for cell therapy, but informed consent should be obtained from patients before hiPSCs are used for the therapy.

Compliance with Ethical Standards

Conflict of interest None.

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