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Review Article

Practical and Ethical Issues Limiting the Clinical Use of Human Embryonic Stem Cells

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Abstract

Stem cell research may revolutionise our understanding of how we develop and function and offer potential treatments for debilitating diseases including Parkinson's disease, spinal cord injury and Huntington's disease. However, Human Embryonic Stem Cell (HESC) research has been surrounded by both ethical and political controversy. The isolation of these pluripotent stem cells has caused arguments regarding the beginning of human personhood. Along with these ethical issues, several practical issues arise in HESC research including immunogenicity issues after transplantation. Legal restrictions in various countries have also hindered the progress of HESC research, creating a difficult environment for advancement in the field. Induced Pluripotent Stem Cells (IPSCs) have offered a potential replacement to HESC research by avoiding the ethical and practical issues associated with HESC. However more research and trials are required to gain a better understanding of their therapeutic mechanism of action and to assess the potential risks and side effects associated with both HESC and IPSC transplants.

ABBREVIATIONS

HESC: Human Embryonic Stem Cells; IPSCs: Induced Pluripotent Stem Cells; UCC: University College Cork; TCD: Trinity College Dublin; RPE: Retinal Pigment Epithelium

INTRODUCTION

The recent breakthrough in stem cell research and the potential of Human Embryonic Stem Cells (HESCs) may lead to many revolutionary procedures and treatments. These potential therapies could be used to help alleviate or possibly cure many degenerative diseases including Parkinson's disease, Huntington's disease and motor neuron disease However, the generation of HESCs have been the centre of controversy in the media and in politics, causing a difference in opinion regarding the use of these cell lines. HESCs are in demand for research because of their ability to be replicated infinite numbers of times *in vitro* and because of their ability to differentiate into any cell type. These characteristics are the cornerstone for development of regenerative medicine and tissue engineering therapies which will be used to replace or repair damaged cells in the human body [1].

Ethical factors affecting HESC research

The removal of pluripotent stem cells from embryos is strongly linked with arguments surrounding the onset of human personhood. Human pluripotent stem cell lines are obtained from the inner cell mass of blastocyst when it is between five and seven days old [1]. However, the removal of these cells often results in the destruction of the embryo. As a result, this is a sensitive and subject which is ethically and politically controversial. Many people believe that an embryo should be considered a person and should be regarded as having the same moral status as any other human being. In religion, for example, the Catholic Church and many other religions believe that "human life begins at conception". Therefore, with this belief, the embryo has interests and rights which demand respect, just like any other human life. This means that the derivation of HESCs from the inner cell mass of the blastocyst could be regarded as murder. However, some other religions such as Judaism argue that life does not begin until implantation of the embryo; therefore, their views are more favourable towards HESC research.

Further ethical issues which have arisen and that have caused several protests is the fact that if this type of research is given the green light, it may be an opening to a slippery slope on dehumanizing practices such as the production of "designer babies" (In which the genetic make-up of the child has been pre-determined to ensure that a particular gene is present), embryo farms and human cloning.

Strict regulations are a necessity in scientific research however; a worrying practice has begun to develop in countries that do not have stringent rules regarding the practical use of stem cell therapy. "Stem Cell Tourism" poses two main threats the advancement of cellular therapy. Firstly, clinics in many locations around the globe are offering patients unregulated "cures" for many debilitating or degenerative diseases with no approval from appropriate agencies such as the U.S FDA or European

equivalents. These treatments are dangerous and misleading to the patients who are spending large amounts of money in the promise of receiving effective treatment for their conditions. Most often the case is they receive a "bogus" treatment with no therapeutic benefit whatsoever. Secondly, clinics operating in this fashion are tainting the public and political opinion on legitimate stem cell therapy by authentic scientists in regulated and respected research facilities [2].

Legal issues affecting HESC research

In Ireland HESC research is currently prohibited, this is because there are no clear guidelines under Irish legislation. HESC research falls under a "grey area" of the law regarding the rights of unborn children because of the nature acquisition of the cells from human embryos [3,4]. Despite these restrictions, two Irish Universities; University College Cork (UCC) and Trinity College Dublin (TCD) have conducted HESC research using cells which were acquired from abroad [5-7].

In 2001 Ex-American President George W. Bush introduced a ban on federal funding on newly created HESCS. This restricted the type of research which was performed by scientists and hindered the sharing of information between scientists. The U.S which was once at the forefront of HESC research at the time could no longer contribute sufficiently to the international field of on-going HESCs research [8]. However, in March 2009, President Obama signed an executive order reversing the previous federal opposition to embryonic stem cell research therefore allowing the U.S scientist more opportunities to expand on their research.

Practical reasons affecting the use of HESCs

Along with these ethical issues, there are many practical and safety issues which must be addressed before implanting these cells. HESCs display several properties which are similar to cancer cells. These consist of the ability to proliferate quickly, expression of oncogenic properties (For example the expression of myc , a common oncogene was able to start the embryonic stem cell model but also caused the formation of cancer cells) and a high level of telomerase activity [9]. Therefore, it is extremely important that these factors are taking into consideration and carefully mediated for the development of safe and effective treatment methods.

One of the fundamental tests for pluripotent human stem cells is the formation of teratomas when injected into a laboratory test animal. Because of the nature of the cells, there is a risk that the formation of these cells mass could occur in human patients and form malignant tumours; therefore, it is important that we can control the proliferation and differentiation of these cells before allowing them to be transplanted [9-11].

One major setback with HESCs is that it has been demonstrated experimentally that when implanted ESCs differentiate *in vivo,* their immunogenicity can be drastically increased [12]. This means that many patients would have to be treated using immune suppressing drugs to fight the body's attempt to reject these newly transplanted cells. This can increase the risk of liver and renal toxicity and immunodeficiency [13].

Alternatives to HESCs treatment

Due to all the factors whether they are ethical, physical, legal or political regarding the use of HESCs, scientists have pursued other avenues to develop cell based treatments for various diseases. Induced Pluripotent Stem Cells (IPSCs) are pluripotent cells derived from regular somatic cells such as fibroblasts. These cells demonstrate very similar characteristics as seen in HESCs and because these cells are derived from adult donors they are not subject to the ethical scrutiny as HESCs. IPSCs also have practical benefits because a personalised treatment can be theoretically provided for the patient using their own cells eliminating the risk of immune rejection. However there have been some studies which have shown that there is a possibility of an immune response [14].

DISCUSSION AND CONCLUSION

The use of HESCs in research is still a controversial and sensitive subject with many factors coming into play including ethical, physical, legal and political. These factors have contributed to a hindrance in the progress in HESC research in both the U.S and in Europe. Despite these factors progress is being made in the field and clinical trials are happening for example one study involves the sub-retinal transplantation of HESC-derived retinal pigment epithelium (RPE) in patients with Stargardt's macular dystrophy and dry age-related macular degeneration. This is the leading cause of blindness in the developing world [15]. Although there has been much progress in alternative methods of creating pluripotent cells through IPSC, there is still much more research needed in this field as many of these cell lines have only been tested in animal test models therefore further research is needed to ensure patients receive a safe and effective treatment.

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