THE CHANGING FACE OF THERAPEUTICS: AN INTRODUCTION TO STEM CELL AND REGENERATIVE THERAPIES

Jason Seewoodhary*
Department of Diabetes and Endocrinology
University Hospital of Wales
Heath Park
Cardiff
CF14 4XN
United Kingdom

ABSTRACT

Stem cell therapies are revolutionizing therapeutics by providing a curative approach to diseases for which, until very recently, symptomatic treatments were only available. This review will critically consider the multidisciplinary role, use and implications of embryonic, adult, and induced pluripotent stem cells. The ethical considerations that impact upon their use will also be discussed.

KEYWORDS
Stem Cell; Embryonic Stem Cell; Adult Stem Cell; induced Pluripotent Stem Cell; Ethics

DISCUSSION

Stem cells are primitive undifferentiated cells that have the capacity of unlimited self-renewal without differentiation whilst retaining the potential towards differentiation. There are three main types of stem cells: embryonic stem cells (ES), adult stem cells, and induced pluripotent stem cells (iPS).

ES cells are derived from the inner cell mass of a developing blastocyst, which is a five-day pre-implantation embryo, and are pluripotent, which means they can differentiate into any cell type of endodermal, ectodermal or mesodermal origin. However, ES cells cannot give rise to extra-embryonic structures such as placental, amniotic or chorionic tissues.

* Email: seewoodharyj@hotmail.com
Similar to ES cells, adult stem cells are undifferentiated cells capable of self-renewal, but in contrast to ES cells, they are found within a specific tissue or organ and are *multipotent*; they can only differentiate into more than one cell type of a specific organ. For example, a neural stem cell can differentiate into an astrocyte, oligodendrocyte or a neuron. Adult stem cells are synonymously referred to as somatic or progenitor stem cells and despite the nomenclature they can be derived from the embryo or foetus. Adult stem cells have been isolated from different organs, such as the bone marrow, which contains two types of adult stem cells: mesenchymal stem cells (MSCs) and haematopoietic stem cells.

In contrast to ES and adult stem cells, iPSCs are derived from non-pluripotent cells such as adult dermal fibroblasts, which have been transformed using plasmid and viral vectors to transfer genes and transcription factors, such as *Oct3/4, Sox2, Klf4, Nanog*, and *Lin28* into these cells. This functions to genetically ‘reprogramme’ cells from a differentiated non-pluripotent state to an ES cell like undifferentiated pluripotent state [1].

The main advantages of ES, adult, and iPSCs hone in on their potential use for stem cell based regenerative therapies, with the overall aim of repairing or replacing diseased tissues and organs. The ability to use stem cell technology would create a potentially limitless, purified, population of patient- and disease-specific cells, which confer a wide range of clinical benefits. These include: understanding the pathogenesis of disease; facilitating drug discovery; and generating cells for transplantation. These principles can be illustrated using Parkinson’s disease (PD) as an example, where strategies to overcome limitations of conventional symptomatic treatments have employed stem cell based therapies. Using stem cell therapies, the depleted dopaminergic neurons in the substantia nigra can be reconstructed by the transplantation of grafted stem cell derived dopaminergic neurons, stimulating local synapse formation and restoring dopaminergic neurotransmission [2]. Candidate stem cells include ES-, adult-, or iPSCs. The decision on the type of stem cell to use rests upon an understanding of the advantages and disadvantages associated with each type of stem cell. This will now be discussed.

ES cells tend to ‘lead’ on most fronts in regenerative medicine due to their broad developmental potential, which is a reflection of their pluripotent nature. ES cells confer the advantage of being renewable, accessible to genetic modifications, and expandable *in vitro* for lengthy periods. Thus ES cells can be yielded in very high purified quantities for potential regenerative purposes. Furthermore, ES cells are very plastic and can be manipulated to become a cell of any bodily organ. These advantages can be appreciated in a rodent PD model, where it has been shown that transplants of undifferentiated ES cells were able to proliferate and fully differentiate into dopaminergic neurons [3]. However, this was off-set by the disadvantage of ES cells having a high tumourigenic potential, which was significantly reduced when the ES cells were pre-differentiated into dopaminergic neurons *in vitro* before
implantation [3]. Other potential disadvantages of ES cells, which are derived from a donor, include transplant rejection. However, this has not yet been reliably determined in human models of disease.

Advantages of adult stem cells include the potential to be harvested from easily accessible organs and expanded. However, in contrast to ES cells, adult stem cells are rarer in number in mature tissues and this is significant as large numbers of cells are needed for stem cell replacement therapies. Similar to ES cells, adult stem cells have the advantageous capacity to self-renew. In an animal model of PD, adult stem cells could be expanded in vitro for a long time and demonstrated multipotency, differentiating into important neural cell types including dopaminergic neurons [4]. Adult stem cells offer the advantage of having a significantly lower tumorigenic potential relative to ES cells. However, recently, the first example of a donor-derived brain tumour following neural stem cell therapy was reported. This suggests that neuronal stem cells maybe involved in gliomagenesis [5]. Further research is needed to assess the safety of the tumourigenic potential of neural stem cells. Relative to ES cells, disadvantages of adult stem cells include lower degrees of plasticity, expandability, and renewability, coupled with a greater susceptibility to senescence. Furthermore, adult stem cells are invasively harvested e.g. bone marrow aspiration to obtain MSCs.

In comparison to adult stem cells, iP S cells offer the advantage of being more easily and non-invasively harvested. They are useful tools for drug development, modeling diseases in vitro, and for transplantation therapies especially if sourced autologously due to a lower potential for rejection. Disadvantages include their potential to form tumours and a lack of long term data on their stability [1].

Despite the potential benefits of stem cell therapy there is heated opposition towards the role of stem cells in regenerative medicine, which requires consideration of the ethical principles that impact upon the use of stem cells. This will now be discussed.

The derivation of ES cell cultures involves disaggregating the blastocyst. Thus, opponents of ES cell research argue this is unethical because it involves the unjust killing of innocent human beings. The ethical dilemmas of such arguments stems from different perspectives about: when does a human being begin to exist; the moral status of human embryos; and the case of ‘doomed embryos’, that is, spare embryos created after fertility treatment. These ethical principles also encompass questions on whether scientists who use but do not derive ES cells are complicit in the destruction of embryos, the permissibility of cloning human embryos to harvest ES cells, whether there is a moral distinction between creating embryos for research purposes and creating them for reproductive means, and the ethics of creating human / non-human chimeras [6].

The ethical considerations that underlie such arguments on the role and use of ES cells can be predominantly, but not exclusively, viewed from five perspectives.
The first is the deontological view, which is an approach that judges the morality of the criteria that defines an embryo as human and as such deserving of respect [7]. In contrast to deontological views, the consequentialist approach assesses whether the righteousness of using human ES cells for regenerative purposes is determined by its consequences, which are a proportionate assessment of beneficence versus non-maleficence [8].

The liberal view on the use of ES cells considers whether individuality is comparable with development. ‘Liberals’ take the view that it is only the cultivation of individuality, which produces well developed human-beings, which raises the questions as to what point is full moral status ascribed to an embryo. Similarly, the gradualist approach reflects on what determines the appropriate cut off point for embryonic research and whether this is the same point at which full moral status is afforded to the beginning of human life. In contrast to these philosophies, the conservative approach is based on the ethical consideration that conception is the only clear biological point in an embryos development [9].

Relative to ES cells the ethical considerations surrounding the impact of adult stem cells are less involved as they do not involve disaggregating the human blastocyst. However, the use of adult stem cells derived from a foetus confers similar ethical dilemmas as described for ES cells.

The use of iPS cells has added a new dimension to the ethical questions in stem cell debates, which hone in on the issues of consent, privacy, clinical translation and intellectual property rights of iPS cells if derived for clinical purposes. To illustrate this principle, if an iPS cell was transformed into spermatozoa for use in reproductive medicine, what impact would this have on donor consent, concerns about cloning and the rights of a potential child to know its parents? The medical ethical principles of justice, autonomy, beneficence, and non-maleficence must be given due consideration when considering the impact of such therapy on patient care [10].

In conclusion there is an emerging body of evidence to suggest the role and use of stem cells can potentially revolutionise clinical medicine. However, there are considerable hurdles that must be overcome. More debate on the ethical considerations that impact on this is needed, which may possibly change and modernise legislation on stem cell research.

BIBLIOGRAPHY


